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MINIREVIEW

Gut Epithelial Metabolism as a Key Driver of Intestinal Dysbiosis Associated with Noncommunicable Diseases

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ABSTRACT In high-income countries, the leading causes of death are noncommunicable diseases (NCDs), such as obesity, cancer, and cardiovascular disease. An important feature of most NCDs is inflammation-induced gut dysbiosis characterized by a shift in the microbial community structure from obligate to facultative anaerobes such as *Proteobacteria*. This microbial imbalance can contribute to disease pathogenesis by either a depletion in or the production of microbiota-derived metabolites. However, little is known about the mechanism by which inflammation-mediated changes in host physiology disrupt the microbial ecosystem in our large intestine leading to disease. Recent work by our group suggests that during gut homeostasis, epithelial hypoxia derived from peroxisome proliferator-activated receptor γ (PPAR-γ)-dependent β-oxidation of microbiota-derived short-chain fatty acids limits oxygen availability in the colon, thereby maintaining a balanced microbial community. During inflammation, disruption in gut anaerobiosis drives expansion of facultative anaerobic *Enterobacteriaceae*, regardless of their pathogenic potential. Therefore, our research group is currently exploring the concept that dysbiosis-associated expansion of *Enterobacteriaceae* can be viewed as a microbial signature of epithelial dysfunction and may play a greater role in different models of NCDs, including diet-induced obesity, atherosclerosis, and inflammation-associated colorectal cancer.

KEYWORDS *Enterobacteriaceae*, intestinal epithelium, microbiota, noncommunicable diseases, obesity

Infectious diseases, defined as those caused by microorganisms (e.g., bacteria, viruses, fungi, or parasites), were the most common cause of death worldwide in the early 20th century. However, deaths from infectious diseases dramatically declined by the end of the 20th century, resulting in large gains in life expectancy, which could be attributed to significant improvements in sanitation, disease prevention by vaccination, and antibiotic development and use as a first line of treatment for bacterial diseases (1).

Although the impact of infectious diseases has been reduced or eliminated in developed countries, the mortality rate from other causes, namely, noncommunicable diseases (NCDs), has increased significantly (2). NCDs are defined as noninfectious, nontransmissible diseases that may be caused by genetics or behavioral factors and generally have a slow progression and long duration (www.who.int/ncds/en). These include cardiovascular diseases, cancer, chronic respiratory diseases, diabetes, and neurodegenerative diseases such as Alzheimer's disease, among others. The most recent data from the World Health Organization (WHO) state that NCDs kill 41 million people each year, which is equivalent to 71% of all deaths globally (www.who.int/ncds/en). Therefore, NCDs are considered the leading causes of death and disability globally and are estimated to cause a cumulative loss of $47 trillion between 2011 and 2030 (3). In the United States, the top two NCDs, cardiovascular disease and cancer, account for nearly 50% of all deaths. NCDs have long surpassed infectious diseases as the main

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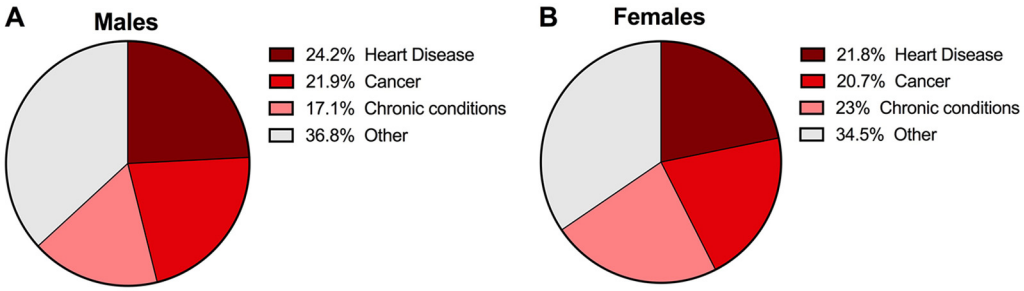

FIG 1 The major current causes of death in the United States are obesity associated noncommunicable diseases. In 2017, the major causes of death in the United States in males (A) and females (B) are cardiovascular disease, followed by cancer and chronic conditions. (Adapted from reference 15 with permission of the publisher.)

cause of death in both male and female Americans (4) (Fig. 1A and B). As a result, NCDs are identified as one of the major health challenges for the 21st century.

The risk factors associated with NCD development can be classified as modifiable behavioral (MB) risk factors and metabolic (ME) risk factors (www.who.int/ncds/en). The MB risk factors for NCDs are tobacco use, physical inactivity, unhealthy diet, and the harmful use of alcohol. ME risk factors arise either from genetic conditions or from MB risk factors and contribute to the four crucial metabolic changes that increase the risk of NCDs: (i) raised blood pressure, (ii) overweight status/obesity, (iii) hyperglycemia, and (iv) hyperlipidemia (2). Overweight status/obesity and elevated blood pressure are the leading ME risk factors responsible for NCD-attributable deaths worldwide (2). Thus, understanding the mechanisms by which major risk factors such as unhealthy diet and obesity contribute to the development and progression of NCDs is key for establishing effective preventive and treatment strategies to manage the 21st century NCD epidemic.

OBESITY IS A MAJOR RISK FACTOR FOR NONCOMMUNICABLE DISEASES

Obesity is a pressing public health problem worldwide, affecting more than 107.7 million children and 603.7 million adults around the globe (5). The incidence of obesity and overweight status has significantly increased in the past decades, and if the rising trends persist, global obesity prevalence is estimated to reach 18% in men and over 21% in women by 2025 (6). Strikingly, 20% of the world's adult population is projected to have obese status by 2030 (7). In the United States, the prevalence of obesity surpasses the worldwide average, as the condition affects 39.8% of the adult population and ~20% of school-age children, with an additional 31.8% of the population being considered overweight (www.cdc.gov/obesity/index.html). As a consequence, overweight and obesity are estimated to be linked to nearly 1 in 5 deaths (18.2%) among adults in the United States (8).

Obesity is a complex and multifactorial disease mainly attributed to genetic, behavioral, social, economic, and environmental factors (9). When assessed as an independent factor, the role of genetics in obesity pathogenesis is significantly less than that of the environment (10). Instead, genetic predisposition seems to increase the risk of weight gain if it interacts with other risk factors such as unhealthy diets and inactive lifestyle (11, 12). Indeed, the current global obesity epidemic can be largely attributed to significant changes in dietary habits, including increased consumption of "Western-style" diets, which are energy dense and rich in saturated fats and sugars. The establishment of diet-induced obesity (DIO) mouse models (13) using a high-fat (HF) and caloric-dense diet has been extremely helpful in understanding the mechanisms linking obesogenic dietary habits and the development of NCDs.

Overweight status and obesity strongly correlate with the incidence of several adverse comorbidities, including cardiovascular disease, cancer, and diabetes (14). The link between DIO and NCDs is particularly compelling in cardiovascular disease (CVD), the most common cause of death in the United States (Fig. 1A and B) (15). The majority

of cardiac deaths (64%) are due to coronary heart disease secondary to atherosclerosis (16). Obese individuals are at a significantly higher risk of developing CVD (www.cdc.gov/obesity/index.html). Obesity and atherosclerosis share pathophysiological pathways, as both are chronic inflammatory conditions characterized by lipid storage imbalance and activation of the immune system (17, 18). Therefore, the study of the mechanisms linking DIO and CVD has a remarkable potential in aiding in the development of novel treatment strategies.

Numerous cancers are associated with excess body weight, and the American Cancer Society suggests that obesity is responsible for about 8% of all cancers in the United States, as well as about 7% of all cancer-related deaths (19). Obese individuals are at higher risk of developing colorectal cancer, breast cancer, and cancer of the endometrium, esophagus, kidney, and pancreas (20). High-income countries, including the United States, have reported a significant rise in the incidence of early-onset colorectal cancer (21–23), a trend that could be partially attributed to the obesity epidemic (23). Experimental studies using preclinical mouse models indicate that obesity and Western-style high-fat diet (HFD) accelerate the multistage transition from normal tissue to invasive malignancy and metastatic disease (24). Taken together, these studies point to the urgency of establishing new prevention and treatment measurements for the current obesity epidemic and obesity-associated cancers.

A new player in the development and progression of NCDs is the intestinal microbiota, also referred to as the "microbial organ" (25, 26). Recent data suggest that gut microbes and their metabolites can affect disease progression through multiple mechanisms, including altering the immune response (reviewed in reference 27), changing host-cell metabolic state (28), and even affecting response to immunotherapy (29). Undeniably, the potential causative role of gut microbiota in obesity represents one of the most extraordinary findings of the past decade. Therefore, the impact of changes in the intestinal microbial community in the pathogenesis of obesity-related NCDs is an extremely relevant and emerging field (30). However, we are only just beginning to understand the mechanisms by which risk factors associated with NCDs promote changes in the intestinal physiology and gut microbiota and how these changes may contribute to NCD pathogenesis.

An important feature of most NCD is inflammation-induced disruption of the intestinal microbiota (dysbiosis), characterized by a shift in the microbial community structure from obligate to facultative anaerobes such as *Enterobacteriaceae* (31) (Fig. 2). In this review, we will explore the potential mechanisms causing *Enterobacteriaceae* expansion in the inflamed gut and during diet-induced obesity. Moreover, we will discuss the role of facultative anaerobic bacteria intestinal bloom in the pathogenesis of obesity-associated NCDs, namely, cardiovascular disease and colorectal cancer.

ROLE OF *ENTEROBACTERIACEAE* EXPANSION IN THE PATHOGENESIS OF OBESITY-ASSOCIATED NCDs

The human large intestine is home to a large and complex bacterial ecosystem, composed mostly of anaerobic organisms. This balanced microbial community (microbiota) performs multiple beneficial functions for the host such as immune education, nutrition, and protection against invasion by enteric pathogens (32).

In the healthy large intestine, *Enterobacteriaceae* is a minor constituent of microbiota (33). However, a wide range of human NCDs are associated with a severe disruption of the balanced gut microbial ecosystem, often characterized by an expansion of facultative anaerobic *Enterobacteriaceae* (31) (Fig. 2). Indeed, a disturbance of the intestinal microbial community by antibiotic treatment results in a dysbiotic outgrowth of facultative anaerobic *Enterobacteriaceae* in humans (34, 35) and murine models (36–38). Intestinal inflammation triggered by genetic predisposition, chemicals, or infection with enteric pathogens causes an uncontrolled luminal expansion of *Enterobacteriaceae* in mouse models (39–43). An intestinal bloom of *Enterobacteriaceae* is also observed in humans with severe intestinal inflammation, including patients with inflammatory bowel disease (44–47), colorectal cancer (48, 49), or necrotizing enterocolitis (50), or

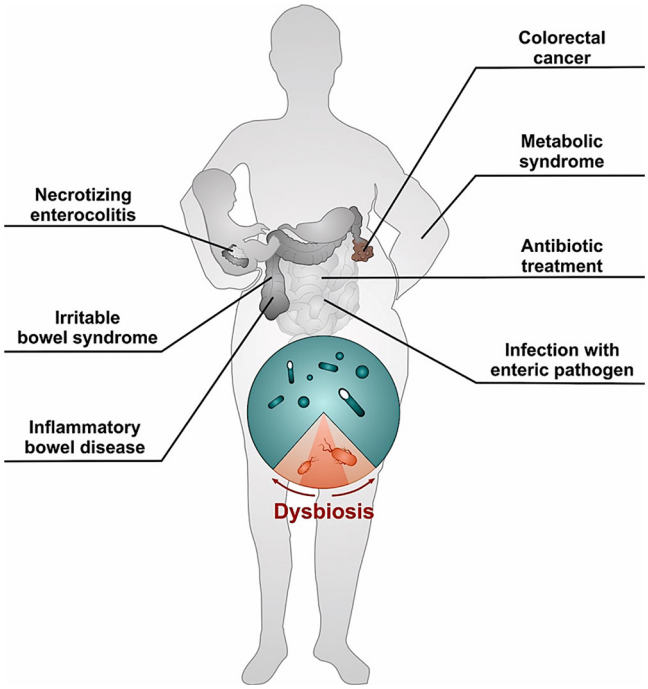

FIG 2 Noncommunicable diseases are linked to intestinal dysbiosis. In the healthy gut, the intestinal microbiota is dominated by obligate anaerobic bacteria (teal). An important feature of most noncommunicable diseases is inflammation-induced gut dysbiosis characterized by a shift in the microbial community structure from obligate to facultative anerobic bacteria (red) such as *Enterobacteriaceae*.

during conditions of low-level intestinal inflammation, such as irritable bowel syndrome (51, 52). Taken together, these studies suggest that *Enterobacteriaceae* expansion may play an important role in the pathogenesis of NCDs (31).

Role of *Enterobacteriaceae* expansion in the pathogenesis of cardiovascular disease. Obesity is considered a key underlying risk factor for many NCDs, including heart disease (53, 54). A Western-style HFD is thought to increase the risk for cardiovascular disease due to systemic hyperlipidemia characterized by increased circulating levels of low-density lipoprotein (LDL) and cholesterol (55). Additionally, Western-style HFD-mediated changes in intestinal microbiota composition have been linked to cardiovascular disease (56, 57). For example, several studies have demonstrated the role of HFD-induced elevated plasma lipopolysaccharide (LPS) levels, a major component of the Gram-negative bacterial outer membrane, in promoting atherosclerosis (58–60). Activation of Toll-like receptor 4 (TLR4) by the lipid A portion of LPS in endothelial cells results in the recruitment of inflammatory monocytes. Once inside the subendothelial space, the recruited inflammatory monocytes become activated macrophages, partially via an LPS/TLR4-dependent mechanism, and help promote the development of the atherosclerotic plaque (61).

Microbiota-derived metabolites may also contribute to the pathogenesis of cardiovascular disease. Recent studies have described the ability of members of the gut microbiota to catabolize dietary choline into trimethylamine (TMA) and acetaldehyde (62). TMA is absorbed in the intestine and oxidized in the liver to trimethylamine *N*-oxide (TMAO), a metabolite that promotes atherosclerosis via the formation of foam cells and atherogenic plaque (63, 64) through poorly identified mechanisms. Interestingly, the *cut* operon containing the gene cluster responsible for choline utilization and TMA production is commonly found in facultative anaerobic *Enterobacteriaceae* such as *Proteus mirabilis* and *Escherichia coli* (62, 65, 66). Choline degradation is thought to occur under anaerobic conditions in a bacterial microcompartment, a protein shell that encloses enzymes and protects the bacterial cell from toxicity of aldehyde intermediates such as acetaldehyde in the case of choline metabolism (66). Strikingly, outgrowth

of facultative anaerobic *Enterobacteriaceae* is also described in obese individuals exposed to HFDs (67–70), raising the possibility that HFD-mediated expansion of TMA-producing *Enterobacteriaceae* may play a role in the pathogenesis of obesity-associated cardiovascular disease.

Role of *Enterobacteriaceae* expansion in colorectal cancer pathogenesis. Colorectal cancer is the third most common cancer and the second most common cause of cancer-related death worldwide (71). A recent report from the American Cancer Society states that the incidence of colorectal cancer has significantly increased in young adults (23), especially those who consume HFDs. Strikingly, only about 20% of colorectal cancer cases can be genetically attributed to familial history (72), suggesting that environmental factors such as obesogenic HFDs may play an important role in promoting tumorigenesis.

Overweight status and obesity may contribute to colorectal cancer pathogenesis through multiple concurrent mechanisms, including (i) stimulation of low-level intestinal inflammation; (ii) increased reactive oxygen species (ROS), which may play a role in DNA damage and mutagenesis; and (iii) changes in levels of growth-promoting factors such as insulin and insulin-like growth factor (IGF-1), which are secondary to obesity-associated metabolic syndrome (24, 73). However, despite the advantages in deciphering how obesity may contribute to cancer pathogenesis, the exact mechanisms underlying HFD-induced colorectal cancer risk and recurrence remain unclear.

In addition to the mechanisms described above, HFD-induced intestinal dysbiosis may be an important missing piece of the obesity-colorectal cancer puzzle. A wide body of literature has suggested that the gut microbiota can enhance colorectal cancer development through its impact on tumor-associated inflammation. Recognition of microbial components (e.g., LPS and flagellin) by the innate and adaptive immune system leads to production of proinflammatory cytokines and other inflammatory products which exert the neoplastic effect (74–77).

The carcinogenic effects of commensal gut bacteria can also result from direct effects of microbially derived products. Members of the *Enterobacteriaceae* family are able to produce toxins with carcinogenic properties, including colibactin, a polyketide-derived genotoxin which is able to cause intestinal epithelial cell double-strand breaks (DSBs) and DNA alkylation, which leads to cell cycle arrest and activation of DNA repair pathways, resulting in increased carcinogenesis (78–82). Indeed, members of the *Enterobacteriaceae* family, in particular, *E. coli* (phylogroups B2 and D), *Klebsiella* spp., and *P. mirabilis*, are frequently detected and overrepresented in the microbiota of colorectal cancer (CRC) patients (47–49). Benign polyps developing early in life of patients with familial adenomatous polyposis are covered by patchy bacterial biofilms containing colibactin-producing *E. coli* (83). Additionally, the expression of colibactin biosynthesis genes is highly induced in biopsy specimens from human CRC patients (84), suggesting a key role of the expansion of colibactin-producing *Enterobacteriaceae* in tumor induction.

RESPIRATION AS A STRATEGY FOR *ENTEROBACTERIACEAE* EXPANSION IN THE GUT

A major goal of every organism in the intestinal microbial community is to ensure long-term survival in the gut lumen and to thrive in a nutritionally competitive environment. Therefore, members of the microbiota have evolved a wide range of metabolic pathways, with each microbe employing a different "winning strategy" for nutrient acquisition and utilization (85). Considering the strong evidence of inflammation-associated dysbiosis, one would assume that inflammation may cause a significant change in the metabolic landscape of the gut, leading to accumulation of a novel set of nutrients for which the microbes that inhabit the intestinal lumen will need to compete. Although several studies have started to explore this concept in the context of both infectious and noninfectious inflammatory diseases (Table 1), we are still only beginning to understand the microbial metabolic adaption during inflammation-induced gut dysbiosis.

TABLE 1 Nutrient sources available to *Enterobacteriaceae* during intestinal dysbiosis

Nutrient	Source	Electron acceptor	Species	Reference(s)
Ethanolamine	Host	Tetrathionate	*S.* Typhimurium	86
Lactate	Host	Oxygen	*S.* Typhimurium	87
Glucarate/galactarate	Microbiota	Oxygen and tetrathionate	*S.* Typhimurium, commensal *E. coli*	88
1,2-propanediol	Microbiota	Oxygen, nitrate, tetrathionate	*S.* Typhimurium	90
Succinate	Microbiota	Oxygen, nitrate, tetrathionate	*S.* Typhimurium	91
L-Serine	Diet	Not determined	Adherent-invasive *E. coli*, *C. rodentium*	92, 102

Carbon sources are key for microorganisms to build biomass and thrive in an environment. A strong body of literature suggests that intestinal inflammation causes changes in both host physiology and microbiota composition, which, in turn, generates a unique set of carbon sources that can be used by *Enterobacteriaceae* to outgrow the resident microbiota (Table 1). During inflammation, intestinal epithelial damage is a source of ethanolamine (86) and lactate (87) for the enteric pathogen *Salmonella enterica* serovar Typhimurium. In addition, an influx of inflammatory cells in response to antibiotic treatment can lead to an increased abundance of sugar oxidation products, such as glucarate or galactarate, and utilization of these carbon sources drives a postantibiotic expansion of *E. coli* and *S.* Typhimurium (88).

Metabolites generated by the microbiota also contribute to dysbiotic *Enterobacteriaceae* expansion. *Bacteroidia*, an abundant member of the intestinal microbial community, is able to break down complex carbohydrates and release monosaccharides like rhamnose and fucose (89). Such monosaccharides can be further fermented into 1,2-propanediol (89), which, in turn, is used by *S.* Typhimurium to grow during inflammation (90). Pathogenic *Enterobacteriaceae* can expand in the gut by taking advantage of additional products from *Bacteroidia* glycan metabolism, such as the poorly fermentable dicarboxylic acid succinate (91).

Recent work by Kitamoto et al. shows that intestinal inflammation alters the amino acid availability in the gut lumen (92). As a consequence, pathogenic *Enterobacteriaceae*, such as adherent invasive *E. coli* and *Citrobacter rodentium*, adapt to gut inflammation by reprogramming their metabolism toward amino acid catabolism (92). This work suggests that amino acids derived from diet, the host, or the intestinal microbiota may be a key resource for *Enterobacteriaceae* survival during intestinal dysbiosis. Future work in further exploring the mechanisms by which pathogenic and commensal bacteria may take advantage of this inflammation-dependent amino acid availability to gain a growth advantage in the inflamed gut will be of great interest.

At first glance, it is not obvious why an increased availability of carbon sources specifically favors the growth of *Enterobacteriaceae* over *Clostridia* or *Bacteroidia* during gut dysbiosis. It is important to remember that *Enterobacteriaceae* are facultative anaerobes that can utilize oxygen (O_2) better than obligate anaerobes *Clostridia* or *Bacteroidia* (93). Therefore, elevated availability of oxygen can potentially increase the abundance of facultative anaerobic *Enterobacteriaceae* within the gut-associated microbial community and, at the same time, inhibit growth of highly oxygen-sensitive commensals, also known as "the oxygen hypothesis" (94). Recent work has confirmed that pathogenic and commensal *Enterobacteriaceae* use oxygen to bloom in the gut during infectious and noninfectious colitis (38, 87, 95–97). This body of work provides experimental evidence that *Enterobacteriaceae* takes advantage of the ability to perform aerobic respiration to outcompete the commensal microbiota in the inflamed gut because respiration generates more energy from the catabolism of carbon sources than fermentation (98).

A groundbreaking work by Winter et al. was the first to reveal that gut inflammation leads to the generation of alternative electron acceptors, which promote anaerobic respiration of *Enterobacteriaceae* (99). In this study, the authors showed ROS generated by the host inflammatory response oxidized thiosulfate ($S_2O_3^{2-}$) into tetrathionate ($S_4O_6^{2-}$), which, in turn, could be used by *S.* Typhimurium to expand during colitis. Additional work solidified the concept that *Enterobacteriaceae* expands within the

microbiota when electron acceptors for anaerobic respiration become available (Table 1). An elevated mucosal synthesis of inducible nitric oxide synthase (iNOS) triggered during pathogen or chemically-induced colitis in mice leads to the production of nitric oxide (NO), which reacts to form nitrate (NO_3^-) in the gut lumen, thereby driving an uncontrolled expansion of commensal *E. coli* or pathogenic *S.* Typhimurium by nitrate respiration (43, 100).

The impact of the respiration-dependent bloom of *Enterobacteriaceae* in disease pathogenesis has been assessed in mouse models of inflammatory bowel disease and colitis-associated colorectal cancer (CAC). Notably, the use of tungstate to selectively inhibit microbial respiratory pathways, operational only during episodes of inflammation, significantly blunted dysbiotic expansion of colitis and CAC-associated *E. coli* and ameliorated signs of disease (101, 102).

Collectively, these studies give rise to the possibility that respiration plays an important role in *Enterobacteriaceae* intestinal expansion that contributes to the pathogenesis of diet-induced obesity and associated NCDs. Additionally, selectively blocking microbial metabolic pathways that are only active during disease may be an unexplored and very attractive treatment strategy for NCDs.

COLONOCYTE METABOLISM AS A KEY DRIVER OF DYSBIOSIS-ASSOCIATED *ENTEROBACTERIACEAE* BLOOM

An important benefit of the obligate anaerobic microbes that inhabit our large bowel is their ability to digest complex dietary carbohydrates (fiber) into fermentation products that are absorbed by the host (103), contributing to host nutrition (104), immune development (105–108), and niche protection against enteric pathogens (38, 95). In contrast, facultative anaerobic bacteria, such as *Enterobacteriaceae*, do not provide such benefits and may be capable of affecting host nutrition by metabolizing fermentation products to carbon dioxide when oxygen is present (90, 91, 109), as discussed above. Thus, it is very likely that the host has developed strategies to help maintain a diverse intestinal microbial community dominated by obligate anaerobic bacteria that provide benefit by generating fermentation products from fiber, a strategy also known as "microbiota-nourishing immunity" (25, 110).

Recent studies propose that colonic epithelial cells (colonocytes) play a central role in shaping a beneficial microbiota (38, 95) and promoting microbiota-nourishing immunity (Fig. 3). Colonocyte maturation and differentiation require peroxisome proliferator-activated receptor γ (PPAR-γ) (111), a nuclear receptor highly expressed in differentiated colonic epithelial cells of mice and humans (112). PPAR-γ activates mitochondrial β-oxidation of long-chain and short-chain fatty acids, resulting in O_2 consumption through oxidative phosphorylation of fatty acids (113–115). As a consequence, mature colonocytes must consume high levels of O_2 to maintain their oxidative metabolic state, resulting in an O_2 partial pressure of less than 7.6 mm Hg ($<$1% oxygen), a condition known as physiologic epithelial hypoxia (116). Therefore, the highly oxidative metabolism of mature colonocytes limits the amount of O_2 diffusing from the mucosal surface, which helps to maintain an anaerobic environment in the lumen of the large bowel (Fig. 3) (38, 93). Through this mechanism, the colonic epithelium ensures a dominance of beneficial anaerobic microorganisms, thereby maintaining gut homeostasis (93).

The considerations described above suggest that an imbalance in the intestinal microbiota could be caused by an underlying defect in epithelial metabolic functions that maintain homeostasis in the colon (25). The initial studies into mechanisms of gut homeostasis disruption used antibiotic models of microbiota disruption (117), which alters epithelial metabolism via the depletion of the microbial-derived short-chain fatty acids butyrate, propionate, and acetate (38). Butyrate activates PPAR-γ signaling in human epithelial cells (118) to drive the metabolism of surface colonocytes toward mitochondrial β-oxidation of fatty acids (113–115), which is important for maintaining physiologic hypoxia (38). Additionally, short-chain fatty acids inhibit intestinal inflammation by maintaining the regulatory T cell pool in mucosa via the activation of

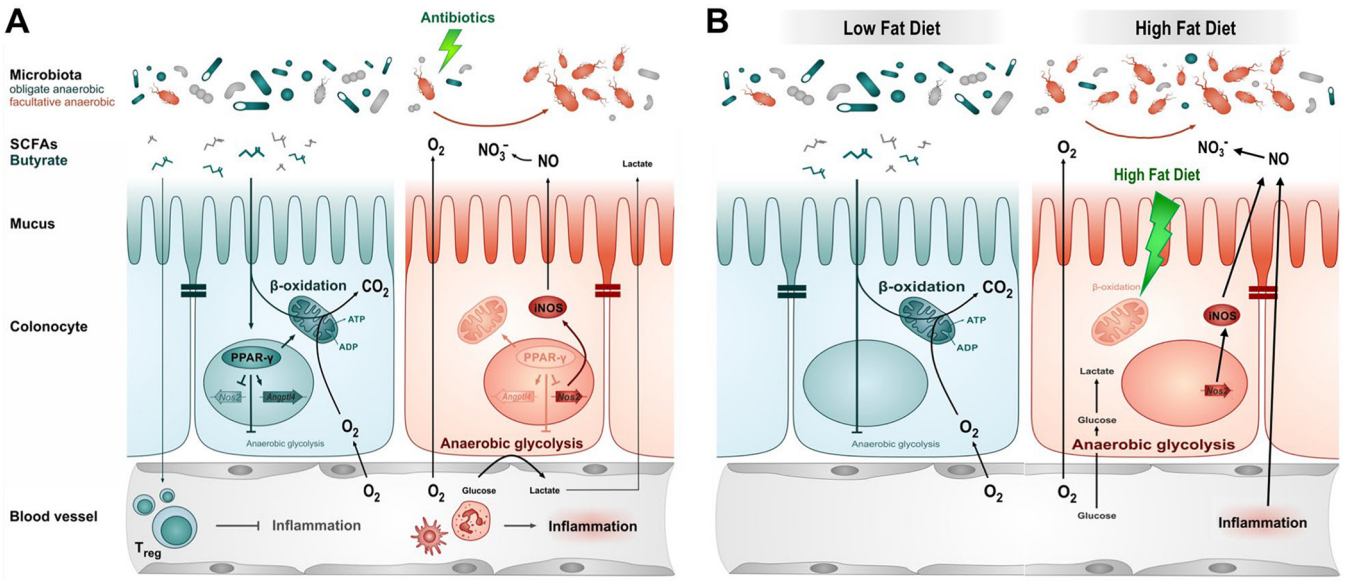

FIG 3 Intestinal epithelial dysfunction contributes to dysbiosis associated expansion of *Enterobacteriaceae*. (A and B, left panels) During gut homeostasis, β-oxidation of microbiota-derived butyrate causes epithelial hypoxia, which supports an anaerobic environment in the lumen of the large intestine. As a consequence, the lack of luminal oxygen drives a dominance of beneficial obligate anaerobic bacteria (green) in the gut microbiota. (A and B, right panels) During gut dysbiosis, colonocytes decrease their oxidative capacity, either due to antibiotic mediated decrease in butyrate-dependent PPAR-γ signaling (A) or due to HFD-induced mitochondrial dysfunction. The resulting epithelial dysfunction disrupts anaerobiosis in the lumen and increases the availability of alternative electron acceptors, driving an expansion of facultative anaerobic *Enterobacteriaceae* by aerobic and anaerobic respiration. SCFAs, short-chain fatty acids.

G-coupled receptors (105–108). As a result, antibiotic treatment increases the inflammatory tone of the colonic mucosa (119) by downregulating epithelial PPAR-γ signaling (38) and decreasing the number of regulatory T cells in the colonic mucosa (105–108). The resulting upregulation of inflammatory signals shifts the metabolism of differentiated colonocytes toward anaerobic glycolysis, a metabolism characterized by low oxygen consumption, high glucose consumption, and high lactate release (38, 87), leading to loss of epithelial hypoxia (117). An important consequence of elevated epithelial oxygenation is an increase in the amount of O_2 emanating from the mucosal surface, providing a key resource for an expansion of facultative anaerobic bacteria by aerobic respiration (Fig. 3A) (38, 120). Importantly, PPAR-γ can inhibit transcription of proinflammatory genes, including the iNOS gene (*Nos2*) (121). Thus, downregulation of PPAR-γ signaling in epithelial cells also results in the elevated synthesis of iNOS, which generates NO to form nitrate (NO_3^-) in the gut lumen, thereby promoting *Enterobacteriaceae* expansion via anaerobic nitrate respiration (38).

Insights into the role of the intestinal epithelium in maintaining gut homeostasis have also come from infectious colitis models (96, 122). *C. rodentium* (family *Enterobacteriaceae*), a mouse enteric pathogen, uses its virulence factors to intimately attach to the colonic surface, creating a favorable niche for competition with the gut microbiota (39, 123). Interestingly, epithelial injury caused by *C. rodentium* virulence factors induces excessive epithelial repair responses, leading to colonic crypt hyperplasia and accumulation of undifferentiated transit-amplifying cells at the mucosal surface (122), which rely on glycolysis for energy production (124). The resulting loss of differentiated colonic epithelial cells increases the amount of O_2 emanating from the mucosal surface and drives growth of *C. rodentium* through aerobic respiration (96).

DIO causes low-grade intestinal inflammation characterized by loss of differentiated epithelial cells and induction of endoplasmic reticulum stress response in colonocytes (125). Systemic hyperglycemia contributes to obesity-associated impairment in intestinal epithelium barrier functions (126). Additionally, consumption of an obesogenic HFD and increased saturated fatty acids may directly affect intestinal epithelial oxidative capacity, impairing mitochondrial bioenergetics by inducing hydrogen peroxide

production in the mitochondria (127, 128). Importantly, recent studies suggest that mitochondria-derived ROS may play a role in reducing gut microbiota diversity (129) through unknown mechanisms. Collectively, these findings raise the possibility that the *Enterobacteriaceae* expansion seen in obesity-driven NCDs may be a result of HFD-induced deterioration of the intestinal epithelial ability to maintain anaerobiosis-driven gut homeostasis (Fig. 3B).

Taken together, the studies described above suggest that an imbalance in the microbial community could be caused by an underlying defect in epithelial immune functions that maintain homeostasis in the colon (25, 130). This concept is particularly important when understanding the mechanisms by which *Enterobacteriaceae* may expand in the gut lumen in a wide range of human diseases (Fig. 2). We now know that the population of facultative anaerobic bacteria blooms in the intestinal lumen during dysbiosis due to a disruption of epithelial physiologic hypoxia, which, in turn, increases the amount of oxygen emanating from the colonic epithelium (131). Additionally, changes in colonic epithelium physiology lead to increased levels of electron acceptors that can be used by *Enterobacteriaceae* for anaerobic respiration (38). Therefore, the colonic expansion of facultative anaerobic bacteria associated with many human NCDs might be caused by a common underlying driver: colonocyte dysfunction.

CONCLUSIONS

Recent research has demonstrated that the gut microbiota, the largest microbial community inhabiting our body, plays a key role in the pathogenesis of a variety of NCDs, especially those associated with obesity. A hallmark of most NCDs is inflammation-induced gut dysbiosis characterized by a shift in the microbial community structure from obligate to facultative anaerobes such as *Enterobacteriaceae*, which may contribute to NCD pathogenesis. However, little is known about how environmental and metabolic factors contribute to obesity-associated dysbiosis. Therefore, further studies on this topic should be of great interest.

The picture emerging from recent studies is that the colonic intestinal epithelium plays a key role in modulating gut microbiota composition, and changes in colonocyte metabolism may be a common driver of disease-associated dysbiosis in the large bowel. Additional work is needed to investigate if changes in the intestinal expansion of *Enterobacteriaceae* observed in individuals consuming a Western-style HFD (67, 69) are driven by an underlying defect in colonic epithelial metabolic function. Nevertheless, the view that colonocyte metabolism plays a key role in balancing the gut microbiota may provide a novel target for therapies to modulate the colonization by members of the microbiota (e.g., colibactin-producing *E. coli* and TMA-producing *Enterobacteriaceae*) that increase the risk for obesity-associated NCDs.

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