Received: 24 June 2020 | Revised: 22 October 2020 | Accepted: 2 November 2020

DOI: 10.1111/omi.12322

REVIEW ARTICLE

WILEY

A double-edged sword: Role of butyrate in the oral cavity and the gut

Xiaoyuan Guan | Wenjing Li | Huanxin Meng

Department of Periodontology, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Peking University School and Hospital of Stomatology, Beijing, China

Correspondence
Huanxin Meng, Department of Periodontology, National Engineering Laboratory for Digital and Material Technology of Stomatology, Beijing Key Laboratory of Digital Stomatology, Peking University School and Hospital of Stomatology, No. 22, Zhongguancun Nandajie, Haidian District Beijing 100081, P.R. China.
Email: kqhxmeng@bjmu.edu.cn

Funding information
National Natural Science Foundation of China Science, Grant/Award Number: 81570980, 81772873 and 81870773

Abstract

Butyrate, a four-carbon short-chain fatty acid (SCFA), is a metabolite of anaerobic bacteria. Butyrate has primarily been described as an energy substance in the studies on the digestive tract. The multiple mechanisms of its protective function in the gut and on underlying diseases (including metabolic diseases, diseases of the nervous system, and osteoporosis) via interaction with intestinal epithelial cells and immune cells have been well documented. There are many butyrogenic bacteria in the oral cavity as well. As essential components of the oral microbiome, periodontal pathogens are also able to generate butyrate when undergoing metabolism. Considerable evidence has indicated that butyrate plays an essential role in the initiation and perpetuation of periodontitis. However, butyrate is considered to participate in the pro-inflammatory activities in periodontal tissue and the reactivation of latent viruses. In this review, we focused on the production and biological impact of butyrate in both intestine and oral cavity and explained the possible pathway of various diseases that were engaged by butyrate. Finally, we suggested two hypotheses, which may give a better understanding of the significantly different functions of butyrate in different organs (i.e., the expanded butyrate paradox).

KEYWORDS
butyrate, gut, oral cavity, periodontitis

1 | INTRODUCTION

Short-chain fatty acids (SCFAs) are saturated aliphatic organic acids with a backbone of one to six carbons that comprise the end products of microbial metabolism. There are two sources of SCFAs: the gut and the oral cavity. One primary site of SCFAs production is the gut, where 400 mmol of SCFAs are synthesized per day (Macfarlane & Gibson, 1994). As a vital contribution of SCFAs, butyrate is of particular interest because it serves as an essential source of energy for the colonic epithelium (Roediger, 1980) and interacts with host cells, including intestinal epithelial cells (IECs) and local immune cells. Furthermore, the protective function of butyrate against diseases, including but not limited to metabolic diseases (Ding et al., 2019; Frank et al., 2007; Knudsen et al., 2019; Sokol et al., 2009; Wang et al., 2012), diseases of the nervous system (Chou et al., 2011; Ferrante et al., 2003; Ryu et al., 2005; Sharma et al., 2015), and the skeleton (Lucas et al., 2018), has been revealed profoundly in recent years.

Periodontal bacteria also release millimolar concentrations of SCFAs into the oral environment (Kurita-Ochiai et al., 1995). The viewpoint that butyrate functions as a pathogenic factor of periodontitis was first introduced by Singer & Buckner in 1981 (Singer & Buckner, 1981). In the next few years, the effects of butyrate on the microorganisms and the cells of gingival tissues were gradually revealed, further indicating that butyrate plays a significant role in the initiation and perpetuation of periodontitis. Also, butyrate acting as a reactivating agent of

latent viruses in the oral cavity brings more insights into the possible functions of butyrate (Imai et al., 2009, 2012).

In this review, we summarize the existing knowledge on the mechanisms of the biological impacts of butyrate in the gut and oral cavity as well as its contribution to the onset and progression of particular diseases. Finally, possible explanations of "the expanded butyrate paradox" are outlined to facilitate further investigations of the precise mechanisms that cause different effects in different sites. Understanding the utterly different functions of the same molecule may bring more insights on how to mitigate the detrimental impacts and enhance the beneficial impacts.

2 | BUTYRATE AND THE GUT

2.1 | Production of butyrate in the gut

SCFAs are converted from polysaccharide, oligosaccharide, protein, peptide, and glycoprotein precursors by fermentation of microorganisms (Cummings & Macfarlane, 1991). Butyrate, as one of the key components of SCFAs, is mainly produced by two predominant families of human colonic Firmicutes, Ruminococcaceae, and Lachnospiraceae, as well as other Firmicutes families, including Erysipelotrichaceae and Clostridiaceae via the phosphotransbutyrylase/butyrate kinase route and butyryl-CoA:acetate CoA-transferase route (Koh et al., 2016; Louis & Flint, 2017; Figure 1).

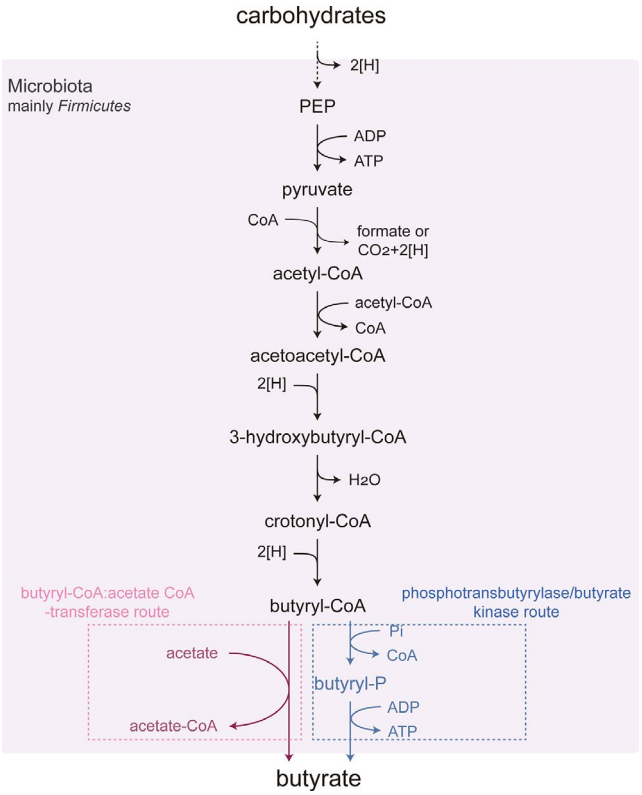

FIGURE 1 Microbial pathways of butyrate synthesis from carbohydrates. Butyrate in the gut is mainly produced by Firmicutes (shown in light purple). The formation of butyryl-CoA from carbohydrates is shown in black. The final step in butyrate synthesis from butyryl-CoA ends with two pathways: phosphotransbutyrylase/butyrate kinase route (shown in blue) and butyryl-CoA:acetate CoA-transferase route (shown in red). The process is linked by arrows, and arrows with dotted lines indicate that several intermediate steps are omitted. CoA, coenzyme A; P, bound phosphate; Pi, inorganic phosphate; PEP, phosphoenolpyruvate; [H] indicates electron carriers [Colour figure can be viewed at wileyonlinelibrary.com]

2.2 | Functions of butyrate in the gut

Gut mucosa constitutes the largest contact surface between the host and the external environment, and it is the most common site of colonization and invasion of susceptible pathogens. Hence, the functional intestine, which could protect against the damaging effect of the bowel contents and block out the harmful substances, is indispensable in maintaining the homeostasis of the internal environment. As an active participant in the intestinal metabolism, butyrate is involved in the enhancement of the mechanical barrier and immune barrier therein (Figure 2).

2.2.1 | Effects on the intestine epithelium

The normal intestine epithelium

The majority of butyrate is absorbed and metabolized in the colon. Subsequently, the colon is the major site that butyrate mainly affects. Butyrate is the preferred fuel of IECs, and an earlier study has demonstrated that the consumption of oxygen in the fermentation of butyrate accounts for 70% of the total oxygen consumption (Wong et al., 2006).

Besides, butyrate is a vital substrate in the maintenance of the integrity of the gut via various pathways. In IECs, butyrate plays an essential role by up-regulating the metabolism, which is mainly mediated through G-protein coupled receptor (GPCR) pathway. For example, proliferation and turnover of IECs in germ-free mice are demonstrated to be promoted by oral administration of SCFAs mediated by the activation of MEK-ERK signaling. Moreover butyrate, a GPR41 agonist (CPC), and a GPR43 agonist (4-CMTB) are all found to promote mouse intestinal organoid development in vitro, which further indicates that butyrate possibly provides stimulation to the proliferative activity and turnover of IECs through GPR41 or GPR43 (Park et al., 2016). It has also been reported that butyrate promotes the antimicrobial peptides in IECs through GPR43, which is mediated by mTOR and STAT3 (Zhao et al., 2018). Apart from the signaling of GPCRs, butyrate can also serve as a protective agent in the following ways. As an energy source of IECs, butyrate has been proven to rescue the deficit in mitochondrial respiration and prevent the occurrence of autophagy in energy-deprived germ-free colonocytes (Donohoe et al., 2011). Although IECs suffer from a low-oxygen condition (He et al., 1999), butyrate is indicated to promote IECs oxygen consumption to the extent which is sufficient to

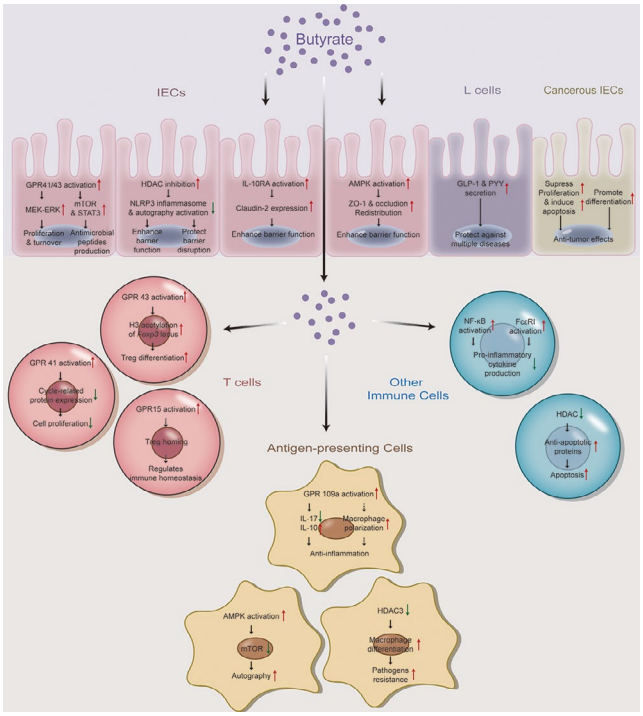

FIGURE 2 Butyrate in the gut affects normal and cancerous intestinal epithelial cells (IECs), L cells, and immune cells. Butyrate works as a vital substrate in maintaining the integrity of the intestinal epithelia via various pathways, including up-regulating the proliferation and turnover of IECs, promoting the production of antimicrobial peptides, enhancing barrier function, and protecting the barrier from disruption. Also, butyrate plays a role in the protection against multiple diseases by acting on L cells and exerts an anti-tumor effect on the cancerous IECs. Additionally, butyrate interacts with multiple types of immune cells, including T cells, antigen-presenting cells, and other immune cells. Butyrate leads to the differentiation of regulatory T cells (Tregs), inhibits cell proliferation of T cells, and plays an anti-inflammatory role by modulating diverse functions of antigens-presenting cells and other immune cells. Solid (proved pathway) and dashed (potential pathway) connecting arrows are shown. Upward-pointing arrows (up-regulation) and downward-pointing arrows (down-regulation) are indicated. GPR, G-protein coupled receptor; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor pyrin domain-containing protein 3; IL, interleukin; AMPK, AMP-activated protein kinase; HDAC, histone deacetylase; NF-κB, nuclear transcription factor-kappa B [Colour figure can be viewed at wileyonlinelibrary.com]

stabilize the hypoxia-inducible factor (HIF; Kelly et al., 2015). Since stabilization of HIF is proven to be a protective factor for murine colitis (Robinson et al., 2008), butyrate augments the epithelial barrier function of the intestine and in underlying disease. Moreover, butyrate may act as a histone deacetylase (HDAC) inhibitor to suppress LPS-induced NLRP3 inflammasome in IECs and serves as an energy source for IECs to inhibit LPS-induced autophagy (Feng et al., 2018). Furthermore, the mutual promoting action between LPS + ATP-activated NLRP3 inflammasome and rapamycin-induced autophagy would lead to the dysfunction of the intestinal barrier, which could be rescued by butyrate treatment (Feng et al., 2018). However, NLRP3 inflammasome and autophagy have been reported to be protective of DDS-induced colitis and Crohn's disease before (Nighot et al., 2015; Zaki et al., 2010). Therefore, the effect that NLRP3 inflammasome and autophagy have on the intestinal barrier remains controversial and needs to be further clarified. Butyrate is also known as an important substance to maintain the epithelium junction. Butyrate activates the interleukin (IL)-10RA-mediated repression of permeability-promoting claudin-2, leading to the promotion of the epithelial barrier formation (Zheng et al., 2017). Butyrate has been shown to accelerate the redistribution of tight junction protein ZO-1 and occludin from the cytoplasm to cell periphery mediated by the activation of AMPK, resulting in the enhancement of the intestinal barrier as well (Peng et al., 2009).

Other than IECs, butyrate has a positive effect on glucagon-like peptide-1 and peptide-YY secretion in colonic L cells (Christiansen et al., 2018), which are closely related to multiple metabolic diseases.

The cancerous intestine epithelium

Butyrate has been shown to have anti-tumor effects in colorectal cancer cells in various studies. This may make it possible for butyrate to act as a therapeutic agent in the future.

Butyrate therapy has been proven effective in several experimental rodent large bowel cancer models because it reduced both the incidence and size of tumors (D'Argenio et al., 1996; Kameue et al., 2004; Medina et al., 1998). However, butyrate serves as an energy source to stimulate cell growth in normal IECs, as mentioned above. The markedly opposing functions of butyrate on the proliferation of normal versus cancerous IECs have been referred to as "butyrate paradox" (Burgess, 2012).

Differences in butyrate metabolism (i.e., the Warburg effect) may result in the paradox (Burgess, 2012). In normal IECs, butyrate functions as the primary fuel for cell metabolism (Roediger, 1980). In contrast, due to the Warburg effect, glucose takes the place of butyrate as the major energy source in cancerous cells. Therefore, butyrate accumulates at a higher dose and functions as an HDAC inhibitor, which would further lead to the inhibition of the proliferation of cancerous IECs (Donohoe et al., 2012). Furthermore, differences in butyrate transport between normal and cancerous cell lines may account for the paradox (Goncalves & Martel, 2016). Butyrate is taken up by monocarboxylate transporter 1 (MCT1) and sodium-coupled monocarboxylate transporter 1 (Goncalves, Araujo et al., 2011; Gupta et al., 2006). Then, butyrate is consumed by efficient cell metabolism and effluxion mediated by breast cancer resistance protein (BCRP) (Donohoe et al., 2012; Goncalves, Gregorio, et al., 2011). In cancerous IECs, butyrate is taken up by MCT1 (Pinheiro et al., 2008), but it is metabolized inefficiently due to the Warburg effect (Burgess, 2012). Moreover, it does not efflux via BCRP-mediated transport (Goncalves, Gregorio, et al., 2011). Thus, it accumulates at higher levels inside of nuclei, which would further lead to HDAC inhibition, thus blocking the apoptosis, proliferation inhibition, and cell differentiating effect mediated by HDAC (Fung et al., 2012; Zhang, Du, et al., 2016).

However, evidence has also shown that butyrate may induce colon cancer under certain circumstances. Belcheva et al. have

demonstrated that butyrate facilitates aberrant proliferation and transformation of colon epithelial cells in $APC^{Min/+}MSH2^{-/-}$ mice (Belcheva et al., 2014). MSH2-deficient colon epithelial cells that have deregulated β-catenin activity may account for the different responses to butyrate that might result in enhanced proliferation and decreased apoptosis (Bordonaro et al., 2008; Lazarova et al., 2004).

2.2.2 | Effects on immune cells

Butyrate plays the role of an immunomodulator by acting on immune cells, including T cells, antigen-presenting cells, monocytes, and neutrophils (discussed below).

Butyrate plays an anti-inflammatory role by exerting an effect mainly on regulatory T cells (Treg cells). As a ligand for GPCRs, butyrate can lead to various cascade effects to regulate the metabolism of T cells by binding different kinds of GPCRs (Sun et al., 2017). For instance, butyrate has been proven to enhance histone H3 acetylation in the promoter and conserved non-coding sequence regions of the Foxp3 locus, leading to the differentiation of Treg cells (Furusawa et al., 2013). A high concentration of butyrate is demonstrated to inhibit cell proliferation by suppression of the multiple cell cycle-related protein expression of Jurkat cells (Kurita-Ochiai et al., 2006). Other studies on GPCRs are also of great interest in providing insights into the interaction between butyrate and Treg cells. As a known ligand of GPCRs, butyrate may enhance Treg cells homing to large intestine lamina propria mediated through GPR15 (Kim et al., 2013), and thereby regulates immune homeostasis in the intestinal mucosa. Other than Treg cells, Coutzac et al. recently demonstrated that oral administration of butyrate appeared to decrease the antitumor activity of anti-CTLA-4 in the mice models and in patients with MM who were treated with ipilimumab by restraining OVA-specific T cell responses following CTLA-4 blockade, which gives us more insights on how systemic butyrate interacts with distant tumor lesions (Coutzac et al., 2020). Butyrate maintaining Th17/Treg cells balance has also been of particular interest in recent years because the balance is vital in immune homeostasis (Zhao et al., 2010). In colorectal colitis rodent models, butyrate has been proven to regulate Th17/Treg cells balance and exert anti-inflammatory effects by inhibiting HDAC1 and blocking the IL-6/STAT3/IL-17 signaling pathway (Zhou, Zhang, et al., 2018; Zhang, Zhou, et al., 2016). An increase in the Th17/Treg cell ratio caused by butyrate is also found in collagen-induced arthritis and autoimmune hepatitis rodent models, which may ameliorate the diseases (Hu et al., 2018; Hui et al., 2019).

GPR109a is a major receptor through which the anti-inflammatory effect could be induced by dendritic cells (DCs) and macrophages. Butyrate-treated DCs or macrophages express higher amounts of IL-10 and reduced amounts of IL-17 production, which enables the differentiation of Treg cells from naïve T cells (Singh et al., 2014). The latest study on GPR109a in Parkinson's Disease (PD) has shown that a lower dose of niacin in PD patients may affect macrophage polarization from M1 (pro-inflammatory) to M2 (counter-inflammatory) profile through the niacin receptor GPR109a (Wakade et al., 2018). This discovery may indicate that butyrate, as a ligand of GPR109a, is also capable of inducing the same effect in the intestine, which still needs verification by further studies. In addition, the GPCR-independent pathway has been found to regulate the transcription of macrophages in vitro. Schulthess et al. found that butyrate blocks mammalian target of rapamycin activity by activating AMP kinase, which would lead to autophagy. On the other hand, HDAC3 inhibition by butyrate drives the differentiation of macrophages, resulting in increased resistance to pathogens (Schulthess et al., 2019). Moreover, attenuation of leukocyte chemotaxis has been found, caused by a reduction of the release of several pro-inflammatory chemokines, including CCL3, CCL4, CCL5, CXCL9, CXCL10, and CXCL11 in human monocyte-derived DCs (Nastasi et al., 2015). The down-regulated leukocyte chemotaxis may weaken the recruitment of leukocytes in the intestine.

In cultured peripheral blood mononuclear cells, butyrate treatment is proven to decrease pro-inflammatory cytokine expression, including tumor necrosis factor (TNF)-α, TNF-β, and IL-1β, via inhibition of NF-κB activation of transcription (Segain et al., 2000). Butyrate is also found to serve as an HDAC inhibitor in immune cells other than T cells. For example, butyrate impedes FcεRI-dependent pro-inflammatory cytokine production (including TNF-α and IL-6) through inhibiting histone deacetylase in mast cells (Zhang, Du, et al., 2016). In addition, it is mentioned that butyrate decreases mRNA expression of multiple anti-apoptotic proteins via histone deacetylase inhibition, thereby causing an increase in caspase cascade-related apoptosis of neutrophils (Aoyama et al., 2010).

2.3 | Butyrate in the gut and diseases

Butyrate in the gut has been proven to be associated with reduced risk of the digestive system and metabolic diseases, including inflammatory bowel diseases (IBDs) and non-alcoholic fatty liver disease (NAFLD).

IBD is a group of multifactorial chronic inflammatory diseases of the gastrointestinal tract comprising two major disorders: ulcerative colitis and Crohn's disease. IBDs have been reported to be associated with decreased butyrate producers by many studies (Frank et al., 2007; Sokol et al., 2009; Wang et al., 2012). Furthermore, butyrate shows effectiveness in colitis treatment (Pacheco et al., 2012; Scheppach et al., 1992). Thus, butyrate may serve as a protective factor against IBDs. As mentioned before, butyrate could be beneficial in the following aspects. (a) Since disruption of the intestinal barrier function is a key characteristic of IBDs, butyrate could protect against IBDs by maintaining epithelial barrier function (Couto et al., 2020) (b) Butyrate can suppress the excess immune response in the gastrointestinal tract (Goncalves et al., 2018; Parada et al., 2019).

NAFLD refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (e.g., heavy alcohol consumption) are present. Butyrate has been indicated to be closely associated with the pathogenesis of NAFLD by many studies (Zhou, Chen, et al., 2018; Ding et al., 2019; Zhou et al., 2017). The mechanisms are

listed as follows. (a) In a mouse model, butyrate increases lipid oxidation by improving the mitochondrial cell energy metabolism in hepatic cells, which would further lead to the reduction of intracellular lipid accumulation (Mollica et al., 2017). (b) Lipopolysaccharide (LPS) has been shown to play an accelerating role in the progression of hepatic steatosis in a rat model (Fukunishi et al., 2014). Considering that butyrate is capable of up-regulating the expression of cell junction proteins (Peng et al., 2009), a decrease of LPS influx and transfer to the liver may occur. In this way, butyrate may impede the progress of NAFLD indirectly. (c) It is reported in vitro and in vivo that butyrate could induce the secretion of GLP-1, which can indirectly prevent NAFLD by increasing fatty acid oxidation, decreasing lipogenesis, and improving hepatic glucose metabolism (Liu et al., 2015).

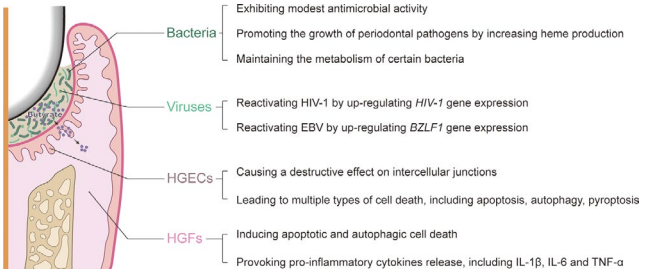

FIGURE 3 Butyrate's effects in the oral cavity on bacteria, viruses, human gingival epithelial cells (HGECs), and Human Gingival Fibroblast (HGFs). HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; TNF, tumor necrosis factor [Colour figure can be viewed at wileyonlinelibrary.com]

3 | BUTYRATE AND THE ORAL CAVITY

3.1 | Production of butyrate in the oral cavity

The main site of butyrate production in the oral cavity lies in the periodontal pocket. In particular, some of the periodontal pathogens, for example, *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum*, release millimolar concentrations of SCFAs as by-products into the environment (Lamont & Jenkinson, 1998; Niederman et al., 1997).

3.2 | Functions of butyrate in the oral cavity

In recent years, apart from investigations on how butyrate affects periodontitis by interacting with microorganisms and host cells, studies on the activating effect that butyrate exerts on latent viruses have also gained much attention. A summary of the main effects of butyrate in the oral cavity is presented in Figure 3.

3.2.1 | Effects on the microorganisms

Bacteria

Both In vitro and in vivo studies have shown that butyric acid and its ester derivatives exhibit antimicrobial activity. Among all the short-chain and mid-chain fatty acids, butyrate exhibits minimal antimicrobial activity in vitro. It only inhibits some gram-positive oral bacteria, for example, *Streptococcus gordonii*; while *P. gingivalis* is resistant to it (Huang, Alimova, et al., 2011). Meanwhile, in a rat model, butyrate is demonstrated to increase heme production. However, the heme-excess condition has opposite impacts on different microbes. Gram-positive bacteria show more sensitivity to heme; thus, these bacteria are more likely to die of rising heme level (Nitzan et al., 1994). On the contrary, excessive heme, which is a vital source of iron, benefits the growth of periodontal pathogens like *P. gingivalis* (Cueno & Ochiai, 2016). Thus, butyrate is identified as a crucial metabolite in providing a competitive advantage to the periodontal pathogens, which is beneficial to the emergence of pathogenic biofilms. In addition, butyrate and its isomer are suitable carbon sources for the maintenance of the metabolism of certain bacteria (Huang, Alimova, et al., 2011). For example, isobutyric acid produced by *P. gingivalis* promotes *T. denticola* growth, which reveals a typical synergistic effect (Huang, Li et al., 2011).

Viruses

As stated before, butyrate can serve as an inhibitory agent of HDAC and lead to the up-regulation of histone hyperacetylation (Sealy & Chalkley, 1978). Similarly, the hyperacetylation of histones due to the treatment of butyrate also promotes the transcription of viral genes in virus-infected oral epithelial cells, which would lead to an end of latency and the reactivation of the virus. Imai and his colleagues have demonstrated that a high concentration of butyrate produced by *P. gingivalis* could induce *HIV-1* reactivation by inhibiting HDACs and up-regulating *HIV-1* gene expression in ACH-2 and U1 cells (Imai et al., 2009). The increase of *HIV-1* gene expression would play a contributing role in HIV progress. Another study of Imai and his colleagues have found that a high concentration of butyrate produced by *P. gingivalis* could also serve as an HDAC inhibitor and enhance *BZLF1* gene expression in EBV-positive human Burkitt's lymphoma cell line and B95-8-221 Luc cells, which could lead to the disruption of viral latency and the reactivation of latent EBV (Imai et al., 2012). In summary, butyrate can modulate the expression of specific viral genes via chromatin modification and thus reactivate the virus.

3.2.2 | Effects on the host

Oral epithelial cells

As a deleterious factor of oral epithelial cells, butyrate can cause damage to the cell junction and lead to cell death via different pathways. Liu and her colleagues have found the downregulation of the expression of various genes related to cell junction, including occluding junctions, anchoring junctions, and communicating junctions after butyrate treatment (Liu et al., 2019). Moreover the latest in vitro study of Magrin et al. have proven that butyrate suppresses intercellular adhesion molecule-1 (ICAM-1) expression in human oral squamous cell

carcinoma cell line HSC-2 (Magrin et al., 2020). This finding may account for the fact that the decrease of ICAM-1 expression in gingival epithelial cells under *P. gingivalis* infection, for butyrate is a known virulence factor of *P. gingivalis* (Huang et al., 2007). However, the difference in cell lines requires further research to verify this fact.

A high concentration of butyrate could result in different types of cell death. It has been shown that butyrate treatment would increase caspase-3 activity, phosphatidylserine redistribution, and decrease anti-apoptotic gene *bcl-2* expression on Ca9-22 cell line, which indicates the apoptosis in human gingival epithelial cells (HGECs). Meanwhile, anti-microtubule-associated protein 1 light chain 3 (LC3), one of the markers of autophagy, was observed to accumulate in the cells, which also suggests the occurrence of autophagic cell death (Tsuda et al., 2010). For the first time, this study has provided evidence that butyrate can lead to cell death in HGECs. Furthermore, Evans et al.'s study on Ca9-22 cells found that butyrate exposure enhancing autophagy is AMPK-dependent (Evans et al., 2017). In the latest study, pyroptosis was also reported to be involved in cell death. After treatment of butyrate, HGECs swelled with the appearance of large bubbles and plasma membrane pores, which indicates pyroptotic cell death. However, the specific pathway remains unknown. At the same time, pyroptotic cell death would provoke an inflammatory response by up-regulating chemokines like IL-8 and monocyte chemotactic protein 1, and releasing intracellular contents into the extracellular microenvironment (i.e., damage-associated molecular patterns) after pyroptotic rupture of the plasma membrane (Liu et al., 2019).

Human gingival fibroblast (HGFs)

Whether butyrate induces apoptosis in HGFs depends on the exposure duration and the inflammatory status of HGFs. Kurita-Ochiai et al. have demonstrated that short-term (24 hr) exposure of high concentration butyrate significantly suppresses the viability of HGFs isolated from persons with periodontitis and induces apoptosis. In contrast, it has no observed effect on HGFs derived from periodontally healthy individuals (Kurita-Ochiai et al., 2008). Subsequently, another further study by Shirasugi has proven that normal HGFs can also respond to butyrate treatment by prolonging exposure time. After long-term exposure of butyrate, normal HGFs would undergo cytostasis and apoptosis as well (Shirasugi et al., 2017).

The mRNA expression of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, is also stimulated by butyrate in HGFs (Shirasugi et al., 2017). TNF-α was up-regulated at the early stage after butyrate treatment, suggesting that it might serve as a trigger of the production of other pro-inflammatory cytokines such as IL-1β and IL-6.

3.3 | Butyrate in the oral cavity and diseases

3.3.1 | Periodontitis

The concept that butyrate contributes to periodontitis was initially postulated by Singer and his colleagues. They first associated SCFAs with periodontitis by demonstrated that SCFAs are pathogenic factors of periodontitis in vitro (Singer & Buckner, 1981), while Kasket conducted in vivo experiments reaffirming the association of SCFAs with periodontitis (Kashket et al., 1996). Of note, many studies have proven that butyrate is involved in the initiation and perpetuation of periodontitis via multiple pathways.

Butyrate rather than lipopolysaccharide plays an essential role in the initiation of periodontitis. Gingival epithelia form the first line of innate defense against various irritants, such as microorganisms and physicochemical factors (Jin, 2011). Therefore, periodontitis is characterized by the breakdown of gingival epithelia. As previously discussed, butyrate can damage gingival epithelia by causing a destructive effect on intercellular junctions, leading to cell death.

Butyrate is also closely related to the perpetuation of periodontitis. Previous studies found that a long-term and high concentration of butyrate exposure leads to apoptotic and autophagic cell death in HGFs (Evans et al., 2017; Kurita-Ochiai et al., 2008). As a vital component of gingival connective tissue, HGFs participate in the production of various intercellular substances, for example, collagen fibers, elastic fibers, and extracellular matrix. Hence, the butyrate-induced cell death of HGFs may cause obstruction of the synthesis of gingival collagen fibers, weakening the gingival barrier and accelerating the progress of periodontitis. Furthermore, numerous pro-inflammatory cytokines released by HGFs (Shirasugi et al., 2017) and chemotactic factors release during the HGFs pyroptosis (Liu et al.., 2019) also provoke chemotaxis and infiltration of other inflammatory cells, which is another deteriorative factor of periodontitis.

3.3.2 | Viral diseases

As stated in the preceding section, butyrate serves as an inhibitor of HDAC and actives the transcription of *BZLF1* gene in EBV-positive cells and *HIV-1* gene in HIV-positive cells (Imai et al., 2009, 2012). The inhibitory effect of butyrate suggests that butyrate can cause latent virus reactivation and accentuate viral infection via chromosome modification.

4 | HYPOTHESES FOR "The Expanded Butyrate paradox"

As mentioned before, the functions of butyrate vary widely in different places. In the gut, butyrate plays a beneficial role by inhibiting the immune response and slowing down the progression of specific diseases. In contrast, butyrate is known as a virulence factor in periodontitis. It has been reported that butyrate has an opposing effect on normal and cancerous colonocytes (i.e., butyrate paradox) (Donohoe et al., 2012). Similarly, butyrate's opposite effects on the gut and the oral cavity are called “the expanded butyrate paradox” (Cueno & Ochiai, 2016).

However, the differences in butyrate functions remain a mystery. The difference in concentration may account for the opposing

effect, as revealed by in vitro studies. Low butyrate levels help maintain colonic health by serving as a fuel for colonocytes and exerting positive effects on the immune cells. On the contrary, a high concentration of butyrate has been reported to lead to cell death of HGFs and HGECs, and reactivation of the latent viruses (Cueno & Ochiai, 2016). Nevertheless, these findings have not been proven in vivo, and the exact concentration of butyrate remains unknown. According to Li's study, the concentration of butyrate in untreated chronic periodontitis is 3.11 ± 1.86 mmol/L (Qiqiang, Huanxin, & Xuejun, 2012). With respect to the gut study, concentrations of different SCFAs measured in gut contents respectively taken from victims who died suddenly show that the concentration of butyrate is estimated to range from 18 to 20 mmol/kg (Macfarlane & Gibson, 1995). However, it may not be appropriate to replace the butyrate concentration of GI fluid by gut contents, so the exact concentration of butyrate in the GI fluid remains unknown.

As regards the opposing functions, the differences in the characteristics of the gut and the oral cavity need to be considered.

4.1 | Difference in the thickness of the mucus layer

Both the gut and the oral cavity are covered by a continuous mucus layer, which is a highly hydrated gel formed by large glycoproteins (i.e., mucins). Mucus can act as a lubricant, a selective barrier, and a defense system (Derrien et al., 2010). The thickness of the mucus layer varies depending on the sites in the gut, ranging from 150–400 μm (a loosely attached mucus layer in the small intestine) to 800–900 μm (a thick mucus layer in the distal colon) (Derrien et al., 2010). In contrast, in the oral cavity, the calculated thickness of the salivary film is 70–100 μm (Collins & Dawes, 1987). The differences in the thickness of the mucus layer could affect the penetration of butyrate, thereby leading to a different concentration on the surface of epithelia (Cueno & Ochiai, 2016).

4.2 | Histological difference in epithelial tissue

Different histological types of epithelial tissue may also be relevant to the expanded butyrate paradox. The intestinal mucosa is composed of a monolayer of column-like epithelia with higher SCFAs permeability (Wong et al., 2006), whereas the oral mucosa is comprised of stratified squamous epithelia that have a lower SCFAs permeability (Cueno et al., 2013). This histological difference may have an effect on the entry and retention of butyrate.

5 | CONCLUSION

To sum up, butyrate, which is a significant microbial by-product, exists and exerts multiple vital effects in both gut and the oral cavity. In the gut, butyrate strengthens the barrier function of the intestine by acting on IECs and immune cells. Thus, butyrate is known as a protective factor in IBDs, NAFLD, obesity, T2DM, diseases of the nervous system, and osteoporosis. On the other hand, butyrate can cause an adverse effect in the oral cavity in the process of periodontitis and viral diseases by affecting microbes and host cells. However, the differences in butyrate function in different body parts still lack a clear explanation. Hence, the investigation of the opposing effects in different sites (i.e., the expanded butyrate paradox) may provide insights into the periodontal treatment by blocking the damaging effect of butyrate or even attempting to exert its protective function in the oral cavity.

ACKNOWLEDGMENT

This work was supported by grants from the National Natural Science Foundation of China Science (81570980, 81772873 and 81870773). We would like to thank Editage (www.editage.cn) for English language editing.

CONFLICT OF INTEREST

The authors have stated that there are no conflicts of interest in connection with this article.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/omi.12322.

ORCID

Xiaoyuan Guan https://orcid.org/0000-0002-0205-5393
Wenjing Li https://orcid.org/0000-0002-9905-3836

REFERENCES

Aoyama, M., Kotani, J., & Usami, M. (2010). Butyrate and propionate induced activated or non-activated neutrophil apoptosis via HDAC inhibitor activity but without activating GPR-41/GPR-43 pathways. *Nutrition*, *26*(6), 653–661. https://doi.org/10.1016/j.nut.2009.07.006

Belcheva, A., Irrazabal, T., Robertson, S. J., Streutker, C., Maughan, H., Rubino, S., Moriyama, E. H., Copeland, J. K., Surendra, A., Kumar, S., Green, B., Geddes, K., Pezo, R. C., Navarre, W. W., Milosevic, M., Wilson, B. C., Girardin, S. E., Wolever, T. M. S., Edelmann, W., … Martin, A. (2014). Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. *Cell*, *158*(2), 288–299. https://doi.org/10.1016/j.cell.2014.04.051

Bordonaro, M., Lazarova, D. L., & Sartorelli, A. C. (2008). Hyperinduction of Wnt activity: A new paradigm for the treatment of colorectal cancer? [Journal Article; Research Support, Non-U.S. Gov't; Review]. *Oncology Research*, *17*(1), 1–9. https://doi.org/10.3727/096504008784046108

Burgess, D. J. (2012). Metabolism: Warburg behind the butyrate paradox? [Comment; Journal Article]. *Nature Reviews Cancer*, *12*(12), 798. https://doi.org/10.1038/nrc3401

Chou, A., Chen, S., Yeh, T., Weng, Y., & Wang, H. (2011). HDAC inhibitor sodium butyrate reverses transcriptional downregulation and ameliorates ataxic symptoms in a transgenic mouse model of SCA3. *Neurobiology of Disease*, *41*(2), 481–488. https://doi.org/10.1016/j.nbd.2010.10.019

Christiansen, C. B., Gabe, M. B. N., Svendsen, B., Dragsted, L. O., Rosenkilde, M. M., & Holst, J. J. (2018). The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. *American Journal of Physiology-Gastrointestinal*

and Liver Physiology, *315*(1), G53–G65. https://doi.org/10.1152/ajpgi.00346.2017

Collins, L. M. C., & Dawes, C. (1987). The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. *Journal of Dental Research*, *66*(8), 1300–1302. https://doi.org/10.1177/00220345870660080201

Couto, M. R., Goncalves, P., Magro, F., & Martel, F. (2020). Microbiota-derived butyrate regulates intestinal inflammation: Focus on inflammatory bowel disease. *Pharmacological Research*, *159*, 104947. https://doi.org/10.1016/j.phrs.2020.104947

Coutzac, C., Jouniaux, J.-M., Paci, A., Schmidt, J., Mallardo, D., Seck, A., Asvatourian, V., Cassard, L., Saulnier, P., Lacroix, L., Woerther, P.-L., Vozy, A., Naigeon, M., Nebot-Bral, L., Desbois, M., Simeone, E., Mateus, C., Boselli, L., Grivel, J., … Chaput, N. (2020). Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. *Nature Communications*, *11*(1), 2168. https://doi.org/10.1038/s41467-020-16079-x

Cueno, M. E., Imai, K., Matsukawa, N., Tsukahara, T., Kurita-Ochiai, T., & Ochiai, K. (2013). Butyric acid retention in gingival tissue induces oxidative stress in jugular blood mitochondria. *Cell Stress and Chaperones*, *18*(5), 661–665. https://doi.org/10.1007/s12192-013-0409-z

Cueno, M. E., & Ochiai, K. (2016). Re-discovering periodontal butyric acid: New insights on an old metabolite. *Microbial Pathogenesis*, *94*, 48–53. https://doi.org/10.1016/j.micpath.2015.10.006

Cummings, J. H., & Macfarlane, G. T. (1991). The control and consequences of bacterial fermentation in the human colon. *Journal of Applied Microbiology*, *70*(6), 443–459.

D'Argenio, G., Cosenza, V., Delle Cave, M., Iovino, P., Delle Valle, N., Lombardi, G., & Mazzacca, G. (1996). Butyrate enemas in experimental colitis and protection against large bowel cancer in a rat model. *Gastroenterology*, *110*(6), 1727–1734. https://doi.org/10.1053/gast.1996.v110.pm8964397

Derrien, M., van Passel, M. W., van de Bovenkamp, H., Schipper, R. G., de Vos, W. M., & Dekker, J. (2010). Mucin-bacterial interactions in the human oral cavity and digestive tract. *Gut Microbes*, *1*(4), 254–268. https://doi.org/10.4161/gmic.1.4.12778

Ding, Y., Yanagi, K., Cheng, C., Alaniz, R. C., Lee, K., & Jayaraman, A. (2019). Interactions between gut microbiota and non-alcoholic liver disease: The role of microbiota-derived metabolites. *Pharmacological Research*, *141*, 521–529. https://doi.org/10.1016/j.phrs.2019.01.029

Donohoe, D. R., Collins, L. B., Wali, A., Bigler, R., Sun, W., & Bultman, S. J. (2012). The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Molecular Cell*, *48*(4), 612–626. https://doi.org/10.1016/j.molcel.2012.08.033

Donohoe, D. R., Garge, N., Zhang, X., Sun, W., O'Connell, T. M., Bunger, M. K., & Bultman, S. J. (2011). The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metabolism*, *13*(5), 517–526. https://doi.org/10.1016/j.cmet.2011.02.018

Evans, M., Murofushi, T., Tsuda, H., Mikami, Y., Zhao, N., Ochiai, K., Kurita-Ochiai, T., Yamamoto, M., Otsuka, K., & Suzuki, N. (2017). Combined effects of starvation and butyrate on autophagy-dependent gingival epithelial cell death. *Journal of Periodontal Research*, *52*(3), 522–531. https://doi.org/10.1111/jre.12418

Feng, Y., Wang, Y., Wang, P., Huang, Y., & Wang, F. (2018). Short-chain fatty acids manifest stimulative and protective effects on intestinal barrier function through the inhibition of NLRP3 inflammasome and autophagy. *Cellular Physiology and Biochemistry*, *49*(1), 190–205. https://doi.org/10.1159/000492853

Ferrante, R. J., Kubilus, J. K., Lee, J., Ryu, H., Beesen, A., Zucker, B., Smith, K., Kowall, N. W., Ratan, R. R., Luthi-Carter, R., & Hersch, S. M. (2003). Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. *Journal of Neuroscience*, *23*(28), 9418–9427. https://doi.org/10.1523/JNEUROSCI.23-28-09418.2003

Frank, D. N., St. Amand, A. L., Feldman, R. A., Boedeker, E. C., Harpaz, N., & Pace, N. R. (2007). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(34), 13780–13785. https://doi.org/10.1073/pnas.0706625104

Fukunishi, S., Sujishi, T., Takeshita, A., Ohama, H., Tsuchimoto, Y., Asai, A., Tsuda, Y., & Higuchi, K. (2014). Lipopolysaccharides accelerate hepatic steatosis in the development of non-alcoholic fatty liver disease in Zucker rats. *Journal of Clinical Biochemistry & Nutrition*, *54*(1), 39–44. https://doi.org/10.3164/jcbn.13-49

Fung, K. Y. C., Ooi, C. C., Lewanowitsch, T., Tan, S., Tan, H. T., Lim, T. K., Lin, Q., Williams, D. B., Lockett, T. J., Cosgrove, L. J., Chung, M. C. M., & Head, R. J. (2012). Identification of potential pathways involved in induction of apoptosis by butyrate and 4-benzoylbutyrate in HT29 colorectal cancer cells. *Journal of Proteome Research*, *11*(12), 6019–6029. https://doi.org/10.1021/pr3007107

Furusawa, Y., Obata, Y., Fukuda, S., Endo, T. A., Nakato, G., Takahashi, D., Nakanishi, Y., Uetake, C., Kato, K., Kato, T., Takahashi, M., Fukuda, N. N., Murakami, S., Miyauchi, E., Hino, S., Atarashi, K., Onawa, S., Fujimura, Y., Lockett, T., … Ohno, H. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*, *504*(7480), 446–450. https://doi.org/10.1038/nature12721

Goncalves, P., Araujo, J. R., & Di Santo, J. P. (2018). A cross-talk between microbiota-derived short-chain fatty acids and the host mucosal immune system regulates intestinal homeostasis and inflammatory Bowel disease. *Inflammatory Bowel Diseases*, *24*(3), 558–572. https://doi.org/10.1093/ibd/izx029

Goncalves, P., Araujo, J. R., & Martel, F. (2011). Characterization of butyrate uptake by nontransformed intestinal epithelial cell lines. *Journal of Membrane Biology*, *240*(1), 35–46. https://doi.org/10.1007/s00232-011-9340-3

Goncalves, P., Gregorio, I., & Martel, F. (2011). The short-chain fatty acid butyrate is a substrate of breast cancer resistance protein. *American Journal of Physiology-Cell Physiology*, *301*(5), C984–C994. https://doi.org/10.1152/ajpcell.00146.2011

Goncalves, P., & Martel, F. (2016). Regulation of colonic epithelial butyrate transport: Focus on colorectal cancer. *Porto Biomedical Journal*, *1*(3), 83–91. https://doi.org/10.1016/j.pbj.2016.04.004

Gupta, N., Martin, P. M., Prasad, P. D., & Ganapathy, V. (2006). SLC5A8 (SMCT1)-mediated transport of butyrate forms the basis for the tumor suppressive function of the transporter. *Life Sciences*, *78*(21), 2419–2425. https://doi.org/10.1016/j.lfs.2005.10.028

He, G., Shankar, R. A., Chzhan, M., Samouilov, A., Kuppusamy, P., & Zweier, J. L. (1999). Noninvasive measurement of anatomic structure and intraluminal oxygenation in the gastrointestinal tract of living mice with spatial and spectral EPR imaging. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(8), 4586–4591. https://doi.org/10.1073/pnas.96.8.4586

Hu, E.-D., Chen, D.-Z., Wu, J.-L., Lu, F.-B., Chen, L. U., Zheng, M.-H., Li, H., Huang, Y. U., Li, J. I., Jin, X.-Y., Gong, Y.-W., Lin, Z., Wang, X.-D., Xu, L.-M., & Chen, Y.-P. (2018). High fiber dietary and sodium butyrate attenuate experimental autoimmune hepatitis through regulation of immune regulatory cells and intestinal barrier. *Cellular Immunology*, *328*, 24–32. https://doi.org/10.1016/j.cellimm.2018.03.003

Huang, C. B., Alimova, Y., Myers, T. M., & Ebersole, J. L. (2011). Short- and medium-chain fatty acids exhibit antimicrobial activity for oral microorganisms. *Archives of Oral Biology*, *56*(7), 650–654. https://doi.org/10.1016/j.archoralbio.2011.01.011

Huang, G. T. J., Haake, S. K., Kim, J. W., & Park, N. H. (2007). Differential expression of interleukin-8 and intercellular adhesion molecule-1 by human gingival epithelial cells in response to *Actinobacillus actinomycetemcomitans* or *Porphyromonas gingivalis* infection. *Molecular Oral Microbiology*, *13*(5), 301–309.

Huang, R., Li, M., & Gregory, R. L. (2011). Bacterial interactions in dental biofilm. *Virulence*, *2*(5), 435–444. https://doi.org/10.4161/viru.2.5.16140

Hui, W., Yu, D., Cao, Z., & Zhao, X. (2019). Butyrate inhibit collagen-induced arthritis via Treg/IL-10/Th17 axis. *International Immunopharmacology*, *68*, 226–233. https://doi.org/10.1016/j.intimp.2019.01.018

Imai, K., Inoue, H., Tamura, M., Cueno, M. E., Inoue, H., Takeichi, O., Kusama, K., Saito, I., & Ochiai, K. (2012). The periodontal pathogen Porphyromonas gingivalis induces the Epstein-Barr virus lytic switch transactivator ZEBRA by histone modification. *Biochimie*, *94*(3), 839–846. https://doi.org/10.1016/j.biochi.2011.12.001

Imai, K., Ochiai, K., & Okamoto, T. (2009). Reactivation of latent HIV-1 infection by the periodontopathic bacterium Porphyromonas gingivalis involves histone modification. *The Journal of Immunology*, *182*(6), 3688–3695. https://doi.org/10.4049/jimmunol.0802906

Jin, L. (2011). An update on innate defense molecules of human gingiva. *Periodontology 2000*, *56*(1), 125–142. https://doi.org/10.1111/j.1600-0757.2010.00364.x

Kameue, C., Tsukahara, T., Yamada, K., Koyama, H., Iwasaki, Y., Nakayama, K., & Ushida, K. (2004). Dietary sodium gluconate protects rats from large bowel cancer by stimulating butyrate production. *Journal of Nutrition*, *134*(4), 940–944. https://doi.org/10.1093/jn/134.4.940

Kashket, S., Zhang, J., & Niederman, R. (1996). Gingival inflammation induced by food and short-chain carboxylic acids. *Journal of Dental Research*, *77*(2), 412–417. https://doi.org/10.1177/00220345980770021001

Kelly, C. J., Zheng, L., Campbell, E. L., Saeedi, B., Scholz, C. C., Bayless, A. J., Wilson, K. E., Glover, L. E., Kominsky, D. J., Magnuson, A., Weir, T. L., Ehrentraut, S. F., Pickel, C., Kuhn, K. A., Lanis, J. M., Nguyen, V. U., Taylor, C. T., & Colgan, S. P. (2015). Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host & Microbe*, *17*(5), 662–671. https://doi.org/10.1016/j.chom.2015.03.005

Kim, S. V., Xiang, W. V., Kwak, C., Yang, Y., Lin, X. W., Ota, M., Sarpel, U., Rifkin, D. B., Xu, R., & Littman, D. R. (2013). GPR15-Mediated homing controls immune homeostasis in the large intestine mucosa. *Science*, *340*(6139), 1456–1459. https://doi.org/10.1126/science.1237013

Knudsen, C., Neyrinck, A. M., Lanthier, N., & Delzenne, N. M. (2019). Microbiota and non-alcoholic fatty liver disease: Promising prospects for clinical interventions? [Journal Article; Research Support, Non-U.S. Gov't; Review]. *Current Opinion in Clinical Nutrition and Metabolic Care*, *22*(5), 393–400. https://doi.org/10.1097/MCO.0000000000000584

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell*, *165*(6), 1332–1345. https://doi.org/10.1016/j.cell.2016.05.041

Kurita-Ochiai, T., Fukushima, K., & Ochiai, K. (1995). Volatile fatty acids, metabolic by-products of periodontopathic bacteria, inhibit lymphocyte proliferation and cytokine production. *Journal of Dental Research*, *74*(7), 1367–1373. https://doi.org/10.1177/00220345950740070801

Kurita-Ochiai, T., Hashizume, T., Yonezawa, H., Ochiai, K., & Yamamoto, M. (2006). Characterization of the effects of butyric acid on cell proliferation, cell cycle distribution and apoptosis. *FEMS Immunology and Medical Microbiology*, *47*(1), 67–74. https://doi.org/10.1111/j.1574-695X.2006.00066.x

Kurita-Ochiai, T., Seto, S., Suzuki, N., Yamamoto, M., Otsuka, K., Abe, K., & Ochiai, K. (2008). Butyric acid induces apoptosis in inflamed fibroblasts. *Journal of Dental Research*, *87*(1), 51–55. https://doi.org/10.1177/154405910808700108

Lamont, R. J., & Jenkinson, H. F. (1998). Life below the gum line: Pathogenic mechanisms of Porphyromonas gingivalis. *Microbiology and Molecular Biology Reviews*, *62*(4), 1244–1263. https://doi.org/10.1128/MMBR.62.4.1244-1263.1998

Lazarova, D. L., Bordonaro, M., Carbone, R., & Sartorelli, A. C. (2004). Linear relationship between Wnt activity levels and apoptosis in colorectal carcinoma cells exposed to butyrate. *International Journal of Cancer*, *110*(4), 523–531. https://doi.org/10.1002/ijc.20152

Liu, J., Wang, G., Jia, Y., & Xu, Y. (2015). GLP-1 receptor agonists: Effects on the progression of non-alcoholic fatty liver disease. *Diabetes/Metabolism Research and Reviews*, *31*(4), 329–335. https://doi.org/10.1002/dmrr.2580

Liu, J., Wang, Y., Meng, H., Yu, J., Lu, H., Li, W., Lu, R., Zhao, Y., Li, Q., & Su, L. I. (2019). Butyrate rather than LPS subverts gingival epithelial homeostasis by downregulation of intercellular junctions and triggering pyroptosis. *Journal of Clinical Periodontology*, *46*(9), 894–907. https://doi.org/10.1111/jcpe.13162

Louis, P., & Flint, H. J. (2017). Formation of propionate and butyrate by the human colonic microbiota. *Environmental Microbiology*, *19*(1), 29–41. https://doi.org/10.1111/1462-2920.13589

Lucas, S., Omata, Y., Hofmann, J., Böttcher, M., Iljazovic, A., Sarter, K., Albrecht, O., Schulz, O., Krishnacoumar, B., Krönke, G., Herrmann, M., Mougiakakos, D., Strowig, T., Schett, G., & Zaiss, M. M. (2018). Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. *Nature Communications*, *9*(1), 55. https://doi.org/10.1038/s41467-017-02490-4

Macfarlane, G. T., & Gibson, G. R. (1994). *Metabolic Activities of the Normal Colonic Flora*. Springer London.

Macfarlane, G., & Gibson, G. (1995). *Physiological and Clinical Aspects of Short-chain Fatty Acids*. Cambridge (England).

Magrin, G. L., Di Summa, F., Strauss, F., Panahipour, L., Mildner, M., Magalhães Benfatti, C. A., & Gruber, R. (2020). Butyrate decreases ICAM-1 expression in human oral squamous cell carcinoma cells. *International Journal of Molecular Sciences*, *21*(5), 1679. https://doi.org/10.3390/ijms21051679

Medina, V., Afonso, J. J., Alvarez-Arguelles, H., Hernandez, C., & Gonzalez, F. (1998). Sodium butyrate inhibits carcinoma development in a 1,2-dimethylhydrazine-induced rat colon cancer. *Journal of Parenteral and Enteral Nutrition*, *22*(1), 14–17. https://doi.org/10.1177/014860719802200114

Mollica, M. P., Mattace Raso, G., Cavaliere, G., Trinchese, G., De Filippo, C., Aceto, S., Prisco, M., Pirozzi, C., Di Guida, F., Lama, A., Crispino, M., Tronino, D., Di Vaio, P., Berni Canani, R., Calignano, A., & Meli, R. (2017). Butyrate regulates liver mitochondrial function, efficiency, and dynamics in insulin-resistant obese mice. *Diabetes*, *66*(5), 1405–1418. https://doi.org/10.2337/db16-0924

Nastasi, C., Candela, M., Bonefeld, C.M., Geisler, C., Hansen, M., Krejsgaard, T., Biagi, E., Andersen, M.H., Brigidi, P., Ødum, N., Litman, T., & Woetmann, A. (2015). The effect of short-chain fatty acids on human monocyte-derived dendritic cells. *Scientific reports*, *5*, 16148.https://doi.org/10.1038/srep16148.

Niederman, R., Buyle-Bodin, Y., Lu, B. Y., Robinson, P., & Naleway, C. (1997). Short-chain carboxylic acid concentration in human gingival crevicular fluid. *Journal of Dental Research*, *76*(1), 575–579. https://doi.org/10.1177/00220345970760010801

Nighot, P. K., Hu, C. A., & Ma, T. Y. (2015). Autophagy enhances intestinal epithelial tight junction barrier function by targeting claudin-2 protein degradation. *Journal of Biological Chemistry*, *290*(11), 7234–7246. https://doi.org/10.1074/jbc.M114.597492

Nitzan, Y., Wexler, H. M., & Finegold, S. M. (1994). Inactivation of anaerobic bacteria by various photosensitized porphyrins or by hemin. *Current Microbiology*, *29*(3), 125–131. https://doi.org/10.1007/BF01570752

Pacheco, R. G., Esposito, C. C., Muller, L. C., Castelo-Branco, M. T., Quintella, L. P., Chagas, V. L., & Schanaider, A. (2012). Use of butyrate or glutamine in enema solution reduces inflammation and fibrosis

in experimental diversion colitis. *World Journal of Gastroenterology*, *18*(32), 4278–4287. https://doi.org/10.3748/wjg.v18.i32.4278

Parada Venegas, D., De la Fuente, M. K., Landskron, G., González, M. J., Quera, R., Dijkstra, G., Harmsen, H. J. M., Faber, K. N., & Hermoso, M. A. (2019). Short Chain Fatty Acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory Bowel diseases. *Frontiers in Immunology*, *10*, 277. https://doi.org/10.3389/fimmu.2019.00277

Park, J.-H., Kotani, T., Konno, T., Setiawan, J., Kitamura, Y., Imada, S., Usui, Y., Hatano, N., Shinohara, M., Saito, Y., Murata, Y., & Matozaki, T. (2016). Promotion of intestinal epithelial cell turnover by commensal bacteria: Role of short-chain fatty acids. *PLoS One*, *11*(5), e156334. https://doi.org/10.1371/journal.pone.0156334

Peng, L., Li, Z. R., Green, R. S., Holzman, I. R., & Lin, J. (2009). Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-Activated protein kinase in Caco-2 cell monolayers. *Journal of Nutrition*, *139*(9), 1619–1625. https://doi.org/10.3945/jn.109.104638

Pinheiro, C., Longatto-Filho, A., Scapulatempo, C., Ferreira, L., Martins, S., Pellerin, L., Rodrigues, M., Alves, V. A. F., Schmitt, F., & Baltazar, F. (2008). Increased expression of monocarboxylate transporters 1, 2, and 4 in colorectal carcinomas. *Virchows Archiv*, *452*(2), 139–146. https://doi.org/10.1007/s00428-007-0558-5

Qiqiang, L., Huanxin, M., & Xuejun, G. (2012). Longitudinal study of volatile fatty acids in the gingival crevicular fluid of patients with periodontitis before and after nonsurgical therapy. *Journal of Periodontal Research*, *47*(6), 740–749. https://doi.org/10.1111/j.1600-0765.2012.01489.x

Robinson, A., Keely, S., Karhausen, J., Gerich, M. E., Furuta, G. T., & Colgan, S. P. (2008). Mucosal protection by hypoxia-inducible factor prolyl hydroxylase inhibition. *Gastroenterology*, *134*(1), 145–155. https://doi.org/10.1053/j.gastro.2007.09.033

Roediger, W. E. (1980). Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut*, *21*(9), 793–798. https://doi.org/10.1136/gut.21.9.793

Ryu, H., Smith, K., Camelo, S. I., Carreras, I., Lee, J., Iglesias, A. H., Dangond, F., Cormier, K. A., Cudkowicz, M. E., H. Brown, R., & Ferrante, R. J. (2005). Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. *Journal of Neurochemistry*, *93*(5), 1087–1098. https://doi.org/10.1111/j.1471-4159.2005.03077.x

Scheppach, W., Sommer, H., Kirchner, T., Paganelli, G.-M., Bartram, P., Christl, S., Richter, F., Dusel, G., & Kasper, H. (1992). Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. *Gastroenterology*, *103*(1), 51–56. https://doi.org/10.1016/0016-5085(92)91094-k

Schulthess, J., Pandey, S., Capitani, M., Rue-Albrecht, K. C., Arnold, I., Franchini, F., Chomka, A., Ilott, N. E., Johnston, D. G. W., Pires, E., McCullagh, J., Sansom, S. N., Arancibia-Cárcamo, C. V., Uhlig, H. H., & Powrie, F. (2019). The short chain fatty acid butyrate imprints an antimicrobial program in macrophages. *Immunity*, *50*(2), 432–445. https://doi.org/10.1016/j.immuni.2018.12.018

Sealy, L., & Chalkley, R. (1978). The effect of sodium butyrate on histone modification. *Cell*, *14*(1), 115–121. https://doi.org/10.1016/0092-8674(78)90306-9

Segain, J. P., De La Blétiere, D. R., Bourreille, A., Leray, V., Gervois, N., Rosales, C., Ferrier, L., Bonnet, C., Blottiere, H. M., & Galmiche, J. P. (2000). Butyrate inhibits inflammatory responses through NFkappaB inhibition: Implications for Crohn's disease. *Gut*, *47*(3), 397–403. https://doi.org/10.1136/gut.47.3.397

Sharma, S., Taliyan, R., & Singh, S. (2015). Beneficial effects of sodium butyrate in 6-OHDA induced neurotoxicity and behavioral abnormalities: Modulation of histone deacetylase activity. *Behavioural Brain Research*, *291*, 306–314. https://doi.org/10.1016/j.bbr.2015.05.052

Shirasugi, M., Nishioka, K., Yamamoto, T., Nakaya, T., & Kanamura, N. (2017). Normal human gingival fibroblasts undergo cytostasis and apoptosis after long-term exposure to butyric acid. *Biochemical and Biophysical Research Communications*, *482*(4), 1122–1128. https://doi.org/10.1016/j.bbrc.2016.11.168

Singer, R. E., & Buckner, B. A. (1981). Butyrate and propionate: Important components of toxic dental plaque extracts. *Infection and Immunity*, *32*(2), 458–463. https://doi.org/10.1128/IAI.32.2.458-463.1981

Singh, N., Gurav, A., Sivaprakasam, S., Brady, E., Padia, R., Shi, H., Thangaraju, M., Prasad, P. D., Manicassamy, S., Munn, D. H., Lee, J. R., Offermanns, S., & Ganapathy, V. (2014). Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity*, *40*(1), 128–139. https://doi.org/10.1016/j.immuni.2013.12.007

Sokol, H., Seksik, P., Furet, J. P., Firmesse, O., Nion-Larmurier, I., Beaugerie, L., Cosnes, J., Corthier, G., Marteau, P., & Doré, J. (2009). Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflammatory Bowel Diseases*, *15*(8), 1183–1189. https://doi.org/10.1002/ibd.20903

Sun, M., Wu, W., Liu, Z., & Cong, Y. (2017). Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. *Journal of Gastroenterology*, *52*(1), 1–8. https://doi.org/10.1007/s00535-016-1242-9

Tsuda, H., Ochiai, K., Suzuki, N., & Otsuka, K. (2010). Butyrate, a bacterial metabolite, induces apoptosis and autophagic cell death in gingival epithelial cells. *Journal of Periodontal Research*, *45*(5), 626–634. https://doi.org/10.1111/j.1600-0765.2010.01277.x

Wakade, C., Giri, B., Malik, A., Khodadadi, H., Morgan, J. C., Chong, R. K., & Baban, B. (2018). Niacin modulates macrophage polarization in Parkinson's disease. *Journal of Neuroimmunology*, *320*, 76–79. https://doi.org/10.1016/j.jneuroim.2018.05.002

Wang, T., Cai, G., Qiu, Y., Fei, N. A., Zhang, M., Pang, X., Jia, W., Cai, S., & Zhao, L. (2012). Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *ISME Journal*, *6*(2), 320–329. https://doi.org/10.1038/ismej.2011.109

Wong, J. M. W., de Souza, R., Kendall, C. W. C., Emam, A., & Jenkins, D. J. A. (2006). Colonic health: Fermentation and short chain fatty acids. *Journal of Clinical Gastroenterology*, *40*(3), 235–243. https://doi.org/10.1097/00004836-200603000-00015

Zaki, M. H., Boyd, K. L., Vogel, P., Kastan, M. B., Lamkanfi, M., & Kanneganti, T.-D. (2010). The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. *Immunity*, *32*(3), 379–391. https://doi.org/10.1016/j.immuni.2010.03.003

Zhang, H., Du, M., Yang, Q., & Zhu, M. (2016). Butyrate suppresses murine mast cell proliferation and cytokine production through inhibiting histone deacetylase. *The Journal of Nutritional Biochemistry*, *27*, 299–306. https://doi.org/10.1016/j.jnutbio.2015.09.020

Zhang, M., Zhou, Q., Dorfman, R. G., Huang, X., Fan, T., Zhang, H., Zhang, J., & Yu, C. (2016). Butyrate inhibits interleukin-17 and generates Tregs to ameliorate colorectal colitis in rats. *BMC Gastroenterology*, *16*(1), 84. https://doi.org/10.1186/s12876-016-0500-x

Zhao, L., Qiu, D. K., & Ma, X. (2010). Th17 cells: The emerging reciprocal partner of regulatory T cells in the liver. *J Dig Dis*, *11*(3), 126–133. https://doi.org/10.1111/j.1751-2980.2010.00428.x

Zhao, Y. E., Chen, F., Wu, W., Sun, M., Bilotta, A. J., Yao, S., Xiao, Y. I., Huang, X., Eaves-Pyles, T. D., Golovko, G., Fofanov, Y., D'Souza, W., Zhao, Q., Liu, Z., & Cong, Y. (2018). GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3. *Mucosal Immunology*, *11*(3), 752–762. https://doi.org/10.1038/mi.2017.118

Zheng, L., Kelly, C. J., Battista, K. D., Schaefer, R., Lanis, J. M., Alexeev, E. E., Wang, R. X., Onyiah, J. C., Kominsky, D. J., & Colgan, S. P. (2017). Microbial-derived butyrate promotes epithelial barrier function through IL-10 receptor-dependent repression of Claudin-2. *Journal of Immunology*, *199*(8), 2976–2984. https://doi.org/10.4049/jimmunol.1700105

Zhou, D. A., Chen, Y.-W., Zhao, Z.-H., Yang, R.-X., Xin, F.-Z., Liu, X.-L., Pan, Q., Zhou, H., & Fan, J.-G. (2018). Sodium butyrate reduces high-fat diet-induced non-alcoholic steatohepatitis through upregulation of hepatic GLP-1R expression. *Experimental & Molecular Medicine*, *50*(12), 1–12. https://doi.org/10.1038/s12276-018-0183-1

Zhou, D. A., Pan, Q., Xin, F.-Z., Zhang, R.-N., He, C.-X., Chen, G.-Y., Liu, C., Chen, Y.-W., & Fan, J.-G. (2017). Sodium butyrate attenuates high-fat diet-induced steatohepatitis in mice by improving gut microbiota and gastrointestinal barrier. *World Journal of Gastroenterology*, *23*(1), 60–75. https://doi.org/10.3748/wjg.v23.i1.60

Zhou, L., Zhang, M., Wang, Y., Dorfman, R. G., Liu, H., Yu, T., Chen, X., Tang, D., Xu, L., Yin, Y., Pan, Y., Zhou, Q., Zhou, Y., & Yu, C. (2018). Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. *Inflammatory Bowel Diseases*, *24*(9), 1926–1940. https://doi.org/10.1093/ibd/izy182

How to cite this article: Guan X, Li W, Meng H. A double-edged sword: Role of butyrate in the oral cavity and the gut. *Mol Oral Microbiol*. 2021;36:121–131. https://doi.org/10.1111/omi.12322