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Short Review

Epigenetic effects of short-chain fatty acids from the large intestine on host cells

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Abstract

Adult humans harbor at least as many microbial cells as eukaryotic ones. The largest compartment of this diverse microbial population, *the gut microbiota,* encompasses the collection of bacteria, archaea, viruses, and eukaryotic organisms that populate the gastrointestinal tract, and represents a complex and dynamic ecosystem that has been increasingly implicated in health and disease. The gut microbiota carries ∼100-to-150-times more genes than the human genome and is intimately involved in development, homeostasis, and disease. Of the several microbial metabolites that have been studied, short-chain fatty acids emerge as a group of molecules that shape gene expression in several types of eukaryotic cells by multiple mechanisms, which include DNA methylation changes, histone post-translational modifications, and microRNA-mediated gene silencing. Butyric acid, one of the most extensively studied short-chain fatty acids, reaches higher concentrations in the colonic lumen, where it provides a source of energy for healthy colonocytes, and its concentrations decrease towards the bottom of the colonic crypts, where stem cells reside. The lower butyric acid concentration in the colonic crypts allows undifferentiated cells, such as stem cells, to progress through the cell cycle, pointing towards the importance of the crypts in providing them with a protective niche. In cancerous colonocytes, which metabolize relatively little butyric acid and mostly rely on glycolysis, butyric acid preferentially acts as a histone deacetylase inhibitor, leading to decreased cell proliferation and increased apoptosis. A better understanding of the interface between the gut microbiota metabolites and epigenetic changes in eukaryotic cells promises to unravel in more detail processes that occur physiologically and as part of disease, help develop novel biomarkers, and identify new therapeutic modalities.

The human microbiota and its composition in adults

Microbial symbionts and their animal hosts have a history of co-evolution that goes back at least 500 million years (Cho and Blaser 2012, Christian *et al.* 2015). Various studies estimated the ratio between eukaryotic and bacterial cells in the human body to be 1:10 (Savage 1977, Bull and Plummer 2014), 1:2–3 (Gilbert 2015), or closer to 1:1 (Sender *et al.* 2016, Sender *et al.* 2016). Until recently, the importance of the human microbiota, previously called *the normal flora* (Cho and Blaser 2012), was largely neglected (Riccio and Rossano 2020), but the topic has received increasing attention, as shown by the exponential growth in the number of papers on the gut microbiota published between 2010 and 2022 (Riccio and Rossano 2020).

The composition of the human microbiota varies by anatomical location and across individuals for the same location, and some of the most extensively studied sites include the skin, the colon, the vagina, the oral cavity, the lung, the stomach, and the hair (Cho and Blaser 2012, Mathieu *et al.* 2018, Lousada *et al.* 2021, Hou *et al.* 2022). The collection of microbial genomes encoded by these bacteria, known as *the human microbiome*, was referred to as *our second genome* (Grice and Segre 2012, Lemm 2018).

The microbiota that colonizes the gastrointestinal tract, also known as *the gut microbiota*, comprises 10^{13}–10^{14} resident microorganisms that include bacteria, archaea, viruses, fungi, and protozoa (Gill *et al.* 2006, Martín *et al.* 2014, Thursby and Juge 2017, Gibiino *et al.* 2021), and represents a highly diverse and dynamic ecosystem with critical roles in human health (Rodríguez *et al.* 2015). Five bacterial phyla dominate the healthy gut microbiota in adults, and each microorganism encodes unique metabolic functions (Bezek *et al.* 2020, Ferraris *et al.* 2020). Most microorganisms that comprise the gut microbiota are in the colon (Jandhyala *et al.* 2015, Gagnière *et al.* 2016, Sender *et al.* 2016, Dieterich *et al.* 2018, Gibiino *et al.* 2021), which is the best studied compartment and one of the most densely populated microbial habitats known on Earth (Kelsen and Wu 2012, Rinninella *et al.* 2019).

As compared to the 24 000 protein-coding genes that are present in the human genome, the gut microbiome collectively contains at least 100-to-150-times more (Hooper and Gordon 2001, Gill *et al.* 2006, Karlsson *et al.* 2013), or >3 million genes, which are involved in a multitude of metabolic pathways (Ursell *et al.* 2012, Valdes *et al.* 2018, Rinninella *et al.* 2019).

The gut microbiota and its link to health and disease

The gut microbiota, relevantly referred to as *foreign to us* while at the same time being *part of us* (Riccio and Rossano 2020), plays critical functions in the biology of the host (Guinane and Cotter 2013), and the two exist in a state of mutual symbiosis (Durack and

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Lynch 2019). Its microbial members interact closely with intestinal epithelial cells, which are located at the interface with underlying host cells. These interactions result in a bidirectional communication between host cells and resident microorganisms as well as microbiota-derived metabolites. Among the several groups of metabolites that are synthesized by the gut microbiota, the most extensively studied ones include short- and branched-chain fatty acids, phenolic derivatives, polyamines, tryptophan, and bile acids (Yang and Kweon 2016, Wilson and Nicholson 2017, Agus *et al.* 2021).

The taxonomical abundance of the gut microbiota and its composition are shaped by factors that include microbial interactions, lifestyle, medication use, social networks, environmental factors, diseases, host genetic factors, and age (Goodrich *et al.* 2014, Blaser 2016, Lane *et al.* 2019, Madison and Kiecolt-Glaser 2019, Amato *et al.* 2021, Herzog *et al.* 2021, Kaur *et al.* 2022). Twin studies suggest that environmental factors, such as diet, outweigh the contribution of genetic factors to the gut microbiota composition and function (Rothschild *et al.* 2018).

The human gut microbiota serves multiple functions in the host. Some of these include its contribution to the structure and function of the intestinal barrier, including that of the mucus layer, which at the same time provides nutrients for the microorganisms (Pickard *et al.* 2017, Paone and Cani 2020); the breakdown of endogenous mucus and the fermentation of non-digestible dietary fibers (Valdes *et al.* 2018), a process that harvests energy and also supports the production of short-chain fatty acids (SCFAs); the metabolism of bile acids (Ramírez-Pérez *et al.* 2017, Valdes *et al.* 2018); the development of the immune system and protection against autoimmune diseases (Wu and Wu 2012, Rosser and Mauri 2016, Schluter *et al.* 2020); the synthesis of lipopolysaccharides, several essential vitamins, such as biotin, folate, and vitamin K, and amino acids (Cummings and Macfarlane 1997, Fan and Pedersen 2021); the breakdown of carcinogens (Morotomi and Mutai 1986, Kho and Lal 2018), xenobiotic compounds, and drugs (Nakov and Velikova 2020); the production of molecules that inhibit potentially pathogenic bacteria (Cipe *et al.* 2015); and the development and functioning of the enteric nervous system (Ochoa-Repáraz and Kasper 2016, De Vadder *et al.* 2018, Geng *et al.* 2022).

The microbiota modulates multiple gut-organ axes, such as the gut-brain, gut-lung, gut-skin, gut-bone, and gut-heart axis (Enaud *et al.* 2020, Afzaal *et al.* 2022, Bulanda and Wypych 2022), and contributes to the development and functioning of the nervous, endocrine, and immune systems (Clarke *et al.* 2014, Obata and Pachnis 2016, Foster *et al.* 2021). Imbalances in the gut microbiota and its metabolites have been implicated not only in gastrointestinal pathologies, but also in extra-intestinal, systemic diseases (Guinane and Cotter 2013, Bull and Plummer 2014, Carding *et al.* 2015, Tang *et al.* 2015, Li *et al.* 2017). Animal and human studies have established links between perturbations in the intestinal microbiota and various medical conditions, including inflammatory bowel disease (Zheng and Wen 2021), Crohn's disease (Manichanh et al. 2006), obesity (Iatcu *et al.* 2021), metabolic syndrome (Iatcu *et al.* 2021) and metabolic diseases (Woting and Blaut 2016), type 2 diabetes (Han and Lin 2014, Gurung *et al.* 2020), cardiovascular disease (Novakovic *et al.* 2020), depression (Winter et al. 2018, Limbana *et al.* 2020, Liu *et al.* 2020), occupational sleep apnea-induced hypertension (Mashaqi and Gozal 2019), Alzheimer's disease (Kowalski and Mulak 2019, Liu *et al.* 2020), Parkinson's disease (Sampson *et al.* 2016, Kang *et al.* 2021, Wang *et al.* 2021), autism spectrum disorder (Rosenfeld 2015), and cancer (Singh *et al.* 2017).

Brief description of epigenetic changes

Among the mechanisms that underlie the communication between the gut microbiota and host cells, the ability of microbial metabolites to epigenetically modulate eukaryotic gene expression has received considerable attention, particularly in recent years (Sharma *et al.* 2019, Woo and Alenghat 2022). The term *epigenetics* was coined by Conrad Waddington in 1942, as a refinement to the concept of *epigenetic landscape* that he introduced earlier (Waddington 1940), to refer to interactions between genes and the environment that shape phenotypes during development (Waddington 1942, Deichmann 2016, Tronick and Hunter 2016). Over the past 80 years, the term itself has developed, along with advances in molecular biology (Choudhuri 2011, Felsenfeld 2014).

Epigenetic changes involve potentially heritable alterations in gene expression without changes in the DNA sequence itself and, in addition to development, are implicated in regulating stem cell potential, tissue homeostasis, the response to environmental factors, and disease pathogenesis (Johnstone and Baylin 2010, Hamilton 2011, Beerman and Rossi 2015, Allis and Jenuwein 2016, Zoghbi and Beaudet 2016, Kang *et al.* 2019). Three major categories of epigenetic changes were described in eukaryotes, and they include DNA methylation, histone post-translational modifications, and RNA interference (RNAi), a process in which microRNAs, a class of non-coding RNA species, inhibit messenger RNA (mRNA) translation (Stephens *et al.* 2013, Du *et al.* 2015, Fessele and Wright 2018, Zhang *et al.* 2019, Aure *et al.* 2021, Liu *et al.* 2022). Proteins and protein complexes that epigenetically modify DNA and histones were classified into epigenetic *writers*, *readers*, and *erasers* (Biswas and Rao 2018). *Writers* include enzymes that deposit epigenetic modifications; *readers* recognize and bind the covalent epigenetic modifications; and *erasers* remove the epigenetic marks (Torres and Fujimori 2015, Biswas and Rao 2018).

DNA methylation, mediated by DNA methyltransferases (DNMTs), involves the covalent attachment of a methyl group to the C-5 position of cytosine in the DNA, leading to the formation of 5-methylcytosine (5-mC) (Jin *et al.* 2011, Schmitz *et al.* 2019). Most instances of cytosine methylation were described when cytosine is part of the CpG dinucleotide, but non-CpG methylation, which refers to cytosine methylation at CpA, CpC, and CpT sites, was also described (He and Ecker 2015, Jang *et al.* 2017). In human somatic cells, >98% of the DNA methylation occurs in the CpG context, and non-CpG methylation is much more abundant in embryonic stem cells (Lister *et al.* 2009, Jin *et al.* 2011). Histone post-translational modifications involve the covalent attachment of functional groups to amino acids, mostly on the N-terminal histone tails, and include acetylation, methylation, phosphorylation, ubiquitylation, SUMOylation, glycosylation, and ADP-ribosylation (Bowman and Poirier 2015, Ramazi *et al.* 2020). Histone acetyltransferases (HATs), sometimes also referred to as lysine acetyltransferases (KATs), comprise a superfamily of enzymes that attach acetyl groups to the ε-amino group of lysine residues on both histone and non-histone proteins, and histone deacetylases (HDACs) (Fig. 1) catalyze the removal of the acetyl groups (Hodawadekar and Marmorstein 2007, Berndsen and Denu 2008, Gong and Miller 2013, Marmorstein and Zhou 2014, Wang *et al.* 2014). An example of acetyl-lysine readers are the bromodomain-containing proteins (Wu *et al.* 2019). Acetylation transforms condensed chromatin into a more relaxed structure, making it more accessible and facilitating gene expression, and deacetylation leads to chromatin compaction, which makes genes less accessible for transcription (Liu and Xu 2004

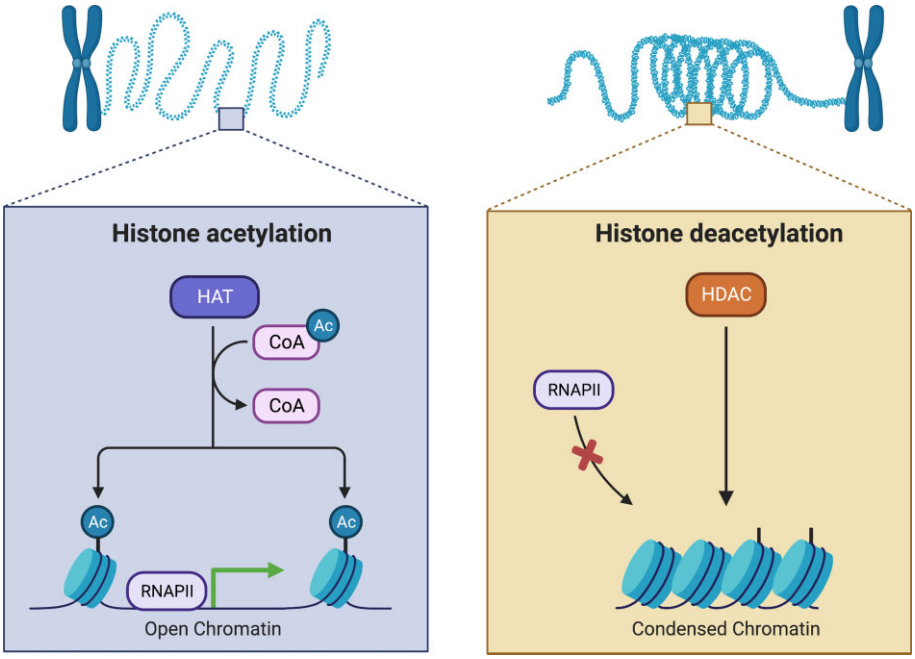

Figure 1. Histone acetylation and deacetylation. The acetylation of histone lysine residues involves the covalent attachment of an acetyl group to the ε-position of the lysine side chain, which creates an open chromatin structure that is more permissible for gene transcription. Lysine deacetylation involves the removal of the acetyl group, leading to a more compacted chromatin structure that is less accessible for active gene expression. Created with BioRender.com.

, Berndsen and Denu 2008, Verza *et al.* 2020). Finally, microRNAs (miRNAs), a class of small non-coding RNAs, are 19–24 nucleotides long single-stranded RNA molecules that regulate gene expression by causing gene silencing or, occasionally, by translational activation (Chuang and Jones 2007, Truesdell *et al.* 2012, Bhaskaran and Mohan 2014, O'Brien *et al.* 2018). Extensive cross-talk was described among different types of epigenetic changes; for example, DNA methylation influences and is influenced by histone post-translational modifications (Miller and Grant 2013, Rose and Klose 2014, Weinberg *et al.* 2019), and microRNAs regulate DNMTs and HDACs (Bourassa and Ratan 2014, Lopez-Bertoni *et al.* 2015).

SCFAs in the large intestine

Based on their carbon chain length, fatty acids are classified as short- (<6C), medium- (6–12C), and long-chain (>12C) (Nogal *et al.* 2021). Short-chain fatty acids (SCFAs) are organic linear carboxylic acids that harbor an aliphatic tail of two to six carbon atoms (Tan et al. 2014, He *et al.* 2020) and are produced in the colon as a result of the anaerobic fermentation of dietary fiber by the gut microbiota (Parada Venegas *et al.* 2019). Acetic acid (C2), propionic acid (C3), and butyric acid (C4) are the most abundant SCFAs in the human large intestine (≥95%) (Fig. 2A) and have received particular attention due to their ability to modulate multiple metabolic pathways relevant to human health (Morrison and Preston 2016, Boets *et al.* 2017, Sun *et al.* 2017, Overby and Ferguson 2021, Portincasa *et al.* 2022). Other SCFAs, such as isovalerate and isobutyrate, are present in only trace amounts (Swer *et al.* 2022).

Different intestinal microbes produce different amounts of SCFAs (Macfarlane and Macfarlane 2003, He *et al.* 2020). In the human large intestine, members of the *Bacteroidetes* synthesize mainly acetate and propionate, and members of the *Firmicutes* mostly produce butyrate (Parada Venegas et al. 2019). The amount and the rate of SCFA production depends on the host species, the composition of the microbiota, the fermentation substrate, and the transit time in the large intestine (Wong et al. 2006). Small amounts of SCFAs originate in the diet (Shimizu *et al.* 2019, He *et al.* 2020), can form by the fermentation of amino acids (Nogal et al. 2021), and are also synthesized in the liver (Tan et al. 2014). Their levels are very low, but measurable, in germ-free animals (Høverstad and Midtvedt 1986). SCFAs enter colonocytes through the apical membrane by passive diffusion and active transport that is mediated by H^+-dependent monocarboxylate transporters (MCTs), previously referred to as solute carrier family (SLC) transporters (Fredericks et al. 2020, Deleu et al. 2021, Portincasa et al. 2022). Colonocytes derive 60%–70% of their energetical needs from oxidizing SCFAs (Roediger 1982, den Besten *et al.* 2013), with butyrate providing their main energy source, and SCFAs that are not used for their energetic needs are transported across their basolateral membrane into the portal vein and, through the peripheral blood, to various organs, where they can be used for metabolic processes or signaling (Sun *et al.* 2017, He *et al.* 2020, Thomas and Denu 2021).

The highest SCFA concentration in the human gastrointestinal tract is in the colon (Parada Venegas *et al.* 2019), where the molar ratio of acetate to propionate to butyrate is about 3:1:1 (Chambers *et al.* 2018, Deleu *et al.* 2021, Nogal *et al.* 2021), but this ratio changes in the peripheral veins to 91:5:4 (Cummings *et al.* 1987). Acetate, more abundant than butyrate and propionate, is the most abundant SCFA in the distal gut and in the systemic circulation (Qin and Wade 2018, Rahman *et al.* 2023). The concentration of SCFAs is about 5-times higher in the portal vein than in the peripheral venous blood, suggesting that the gut is their primary source (Cummings *et al.* 1987). In addition to serving as an energy source for the cells of the colon and ileum (Yao *et al.* 2022), SCFAs influence microbial composition (Overby and Ferguson 2021), pH (Overby and Ferguson 2021), the integrity of the intestinal barrier (Overby and Ferguson 2021), glucose and lipid metabolism (Morrison and Preston 2016, Nogal *et al.* 2021), appetite (Morrison and Preston 2016, Blaak *et al.* 2020), are involved in mucus production (Blaak *et al.*

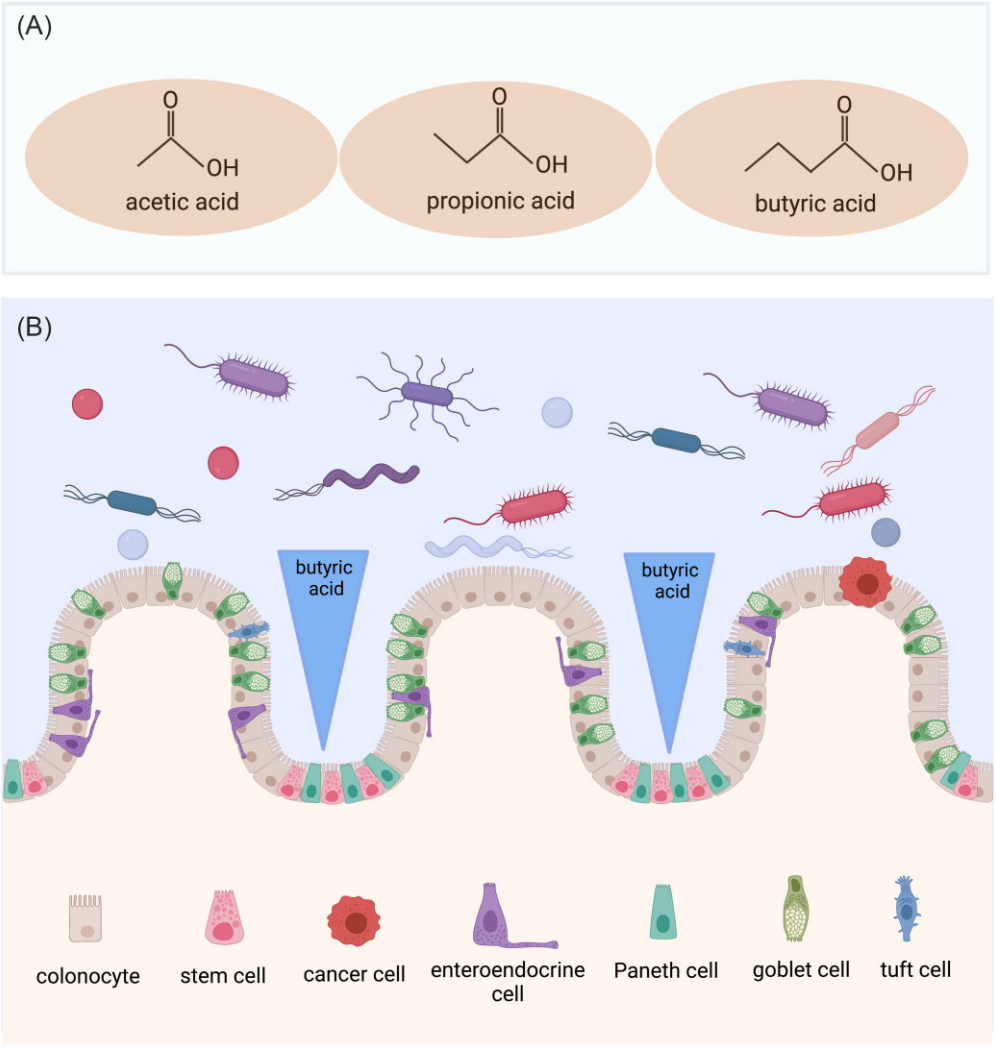

Figure 2. Short-chain fatty acids in the large intestine have important local and systemic biological functions. **(A)** Acetic, propionic, and butyric acid are the three most abundant SCFAs in the large intestine, where they are synthesized by the gut microbiota from dietary fiber. **(B)** Schematic representation of the butyrate paradox. Butyric acid creates a colonic lumen-to-crypt decreasing concentration gradient, which promotes the growth or decreases the proliferation of healthy colonocytes, but selectively inhibits undifferentiated cells, such as cancer cells and stem cells, by mechanisms that include epigenetic changes. Created with BioRender.com.

2020), and regulate inflammation (He *et al.* 2020) and the immune response (Kim *et al.* 2014, Blaak *et al.* 2020, Yao *et al.* 2022).

SCFAs impact histone acetylation

Microbial-derived SCFAs are one of the best understood mediators of the microbiota-host interactions (Fellows and Varga-Weisz 2020) and, along with other metabolites, emerge as important participants to the microbiota-gut-brain axis (Swer *et al.* 2022). In 1978, Sealy and Chalkley reported, in rat hepatoma cells that were treated with SCFAs such as sodium butyrate or acetic, isobutyric, or propionic acid, a global increase in histone acetylation as a result of the noncompetitive and reversible inhibition of HDAC activity (Sealy and Chalkley 1978). The same year, Boffa *et al.* reported that in HeLa cells, sodium butyrate causes an increase in histone acetylation by inhibiting HDAC activity (Boffa *et al.* 1978) and Reeves and Candido found that sodium butyrate suppressed histone deacetylation in Friend erythroleukemic cells in culture (Reeves and Candido 1978).

SCFAs generated in the gut mediate at least part of their local and systemic biological effects by signaling through G protein-coupled receptors (GPCRs), including GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A (HCAR2), inhibiting HDACs, and their influence on cellular energy metabolism (Canani *et al.* 2011, Vinolo *et al.* 2011, Tan *et al.* 2014, Dalile *et al.* 2019, Gasaly *et al.* 2021, Nogal *et al.* 2021). The main HDAC inhibitor is butyric acid, which inhibits mostly HDAC enzymes from classes I, IIa, and IV (Davie 2003, Licciardi *et al.* 2010, Fock and Parnova 2023). While the mechanisms that explain the ability of SCFAs to inhibit HDACs are incompletely understood, it was proposed that they may act directly on the HDAC or indirectly, through GPCR activation (He *et al.* 2020). Butyrate, by being metabolized to acetyl-CoA, also increases histone acetylation (Donohoe *et al.* 2012). An analysis that conducted deep profiling of histone modifications using mass spectrometry and chromatin immunoprecipitation sequencing found reduced histone H4 mono-, di-, and tri-acetylation at gene bodies across the genome of cecal and colonic epithelial cells. Isotope tracing studies using labeled fermentable fiber confirmed that the isotope becomes incorporated into acetylated H4 and H3, support-

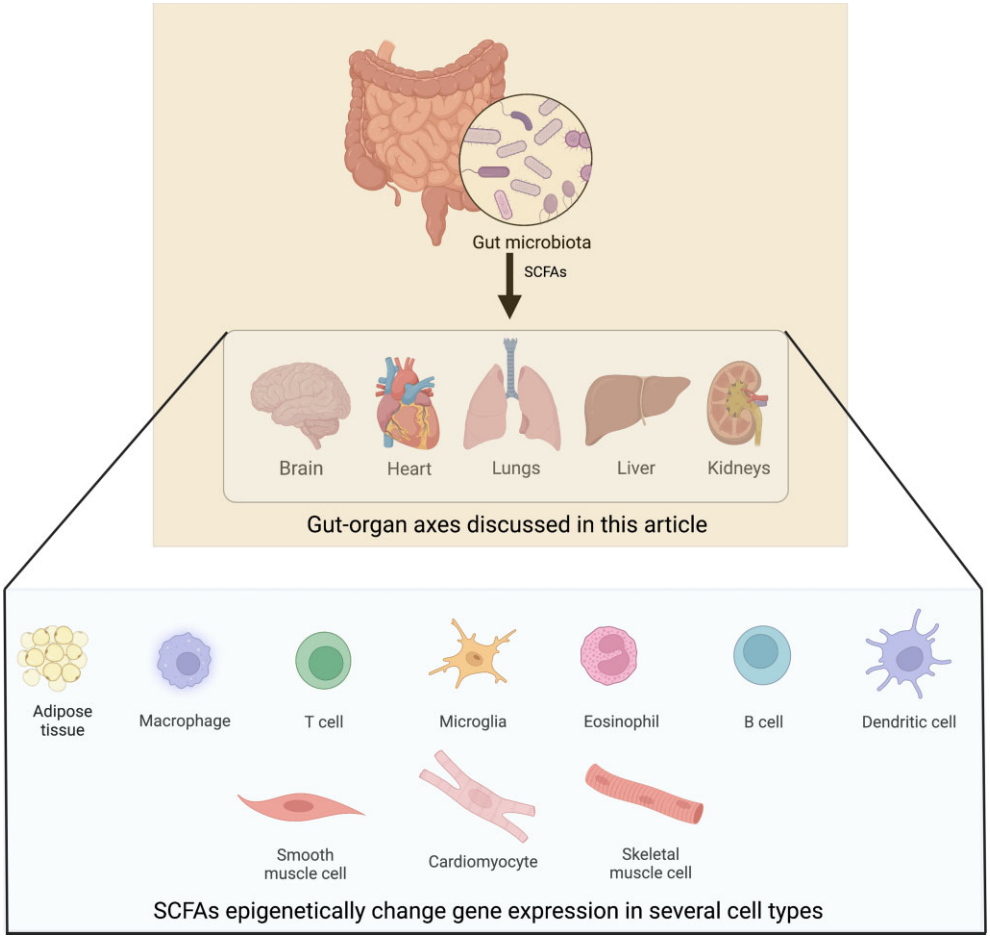

Figure 3. Short-chain fatty acids and some of their target organs and cells. SCFAs generated in the large intestine influence several gut-organ axes and epigenetically modulate gene expression in multiple cell types in the body. Created with BioRender.com.

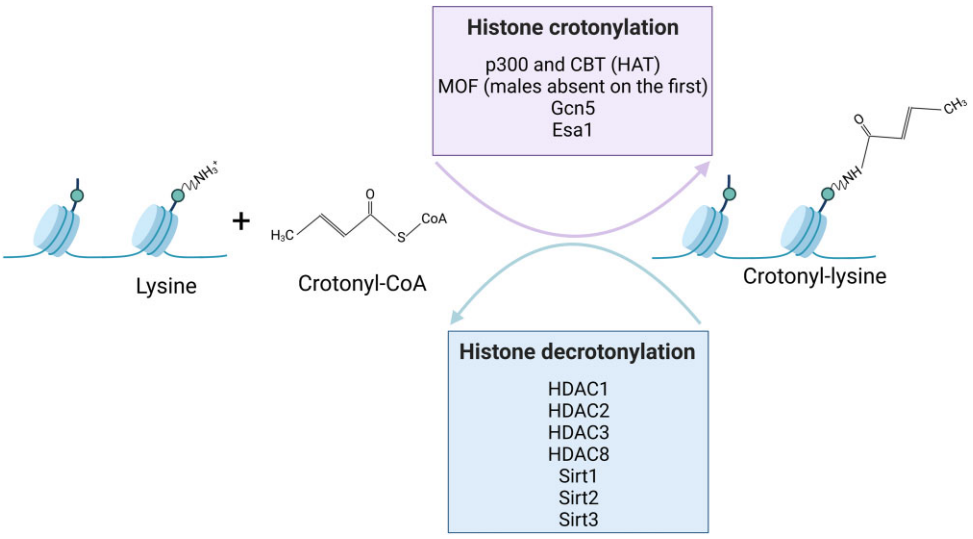

Figure 4. Histone lysine crotonylation, an evolutionarily conserved post-translational epigenetic modification, involves the reversible covalent attachment of a crotonyl group to the ε-amino group of the lysine side chain, and histone lysine decrotonylation involves the removal of the crotonyl group. Several histone acetyltransferases also have histone crotonyltransferase activity, and several histone deacetylases have histone decrotonylation activities as well. Based on information from references (Madsen and Olsen 2012, Bao *et al.* 2014, Sabari *et al.* 2015, Liu *et al.* 2017, Wei *et al.* 2017, Xu *et al.* 2017, Fellows *et al.* 2018, Kollenstart *et al.* 2019). Created with BioRender.com.

ing the view that butyrate generated from fiber, under the influence of the microbiota, provides carbon sources for histone acetylation (Lund *et al.* 2022). Propionate and butyrate also activate the p300 acetyltransferase, which recently emerged as a previously unknown mechanism (Thomas and Denu 2021).

Butyrate, the most studied SCFA (Vinolo *et al.* 2011), is the most potent, and acetate is the least potent HDAC inhibitor (Vinolo *et al.* 2011). The ability of SCFAs to inhibit HDAC activity was shown in the gut epithelium (Li *et al.* 2017, Han *et al.* 2018, Mirzaei *et al.* 2021), the associated immune cells (Chang *et al.* 2014, Kim *et al.* 2016, Schulthess *et al.* 2019, Sanchez *et al.* 2020, Kibbie *et al.* 2021, Ney *et al.* 2023), skeletal (Gao *et al.* 2009) and vascular smooth muscle cells (Mathew *et al.* 2010, Mathew *et al.* 2019, Zhong *et al.* 2022), endothelial cells (Li *et al.* 2018), and cardiomyocytes (Zhang *et al.* 2019, Umei *et al.* 2020), and was documented at several sites in the body, including the central nervous system (Ziemka-Nalecz *et al.* 2017, Reddy *et al.* 2018, Jaworska *et al.* 2019, Silva *et al.* 2020), the kidneys (Liu *et al.* 2021), and the lungs (Folkerts et al. 2020, Karoor *et al.* 2021, Yip *et al.* 2021). In addition to being an HDAC inhibitor, butyrate was linked to DNA methylation changes in eukaryotic cells (de Haan *et al.* 1986, Wippermann *et al.* 2017, Wang *et al.* 2022, Xie *et al.* 2022) and was shown to signal through microRNAs. For example, butyrate decreased the expression of several microRNA clusters in human colon cancer cells (Hu *et al.* 2011, Hu *et al.* 2015), and in mouse and human B cells, butyrate and propionate upregulated microRNAs that targeted the 3'-untranslated region of Aicda/AICDA and Prdm1/PRDM1 mRNAs and dose-dependently inhibited their translation as a result of their HDAC inhibitory activity (Sanchez *et al.* 2020).

The butyrate paradox

The butyric acid that is generated in the colon by microbial fermentation establishes two concentration gradients (Donohoe *et al.* 2012, van Deuren *et al.* 2022, van Deuren *et al.* 2022). A proximal-to-distal concentration gradient occurs because most butyrate is produced in the proximal colon, and the butyrate that is not used by colonocytes for their metabolic requirements travels distally as a result of peristaltic movements (Donohoe *et al.* 2012, Liu *et al.* 2018). A second gradient is generated along the lumen-to-crypt axis (Fig. 2B), with larger butyrate concentrations in the colonic lumen and lower concentrations at the base of the crypts of Lieberkühn (Bultman 2016). Butyrate concentrations are about 5 mM in the colonic lumen of mice (Louis and Flint 2007, Kaiko *et al.* 2016, Vemula and Jala 2016, Linder and Mostoslavsky 2017) and 10–70 mM in the colonic lumen of humans (Cummings *et al.* 1987, Vemula and Jala 2016, Ota and Sakuraba 2022), but were estimated to be 50–800 μM in the mouse colonic crypts (Donohoe *et al.* 2012).

The effects of butyrate on the colonic epithelium are complex and depend on its concentration and on the state of cellular differentiation. While butyrate promotes the growth of healthy colonocytes, or decreases their proliferation, depending on its concentration (Lupton 2004, Comalada *et al.* 2006, Canani *et al.* 2011, Donohoe *et al.* 2012, Li *et al.* 2018, Hajjar *et al.* 2021), it selectively inhibits undifferentiated cells, such as cancer cells (Barnard and Warwick 1993, Archer *et al.* 1998, Gonçalves and Martel 2013) and stem cells (Kaiko *et al.* 2016, Singh *et al.* 2016). In various studies, butyrate inhibited the proliferation of colorectal cancer cells and cell lines in a dose- and time-dependent manner, caused cell cycle arrest mostly in the G_1 phase, increased differentiation, and induced apoptosis (Siavoshian *et al.* 1997, Orchel *et al.* 2005, Hong *et al.* 2015, Ryu *et al.* 2018, Chen *et al.* 2019, Klepinina *et al.* 2021, Salvi and Cowles 2021, Xi *et al.* 2021). This poorly understood duality, which has become known as *the butyrate paradox* (Donohoe *et al.* 2012, Gasaly *et al.* 2021, Salvi and Cowles 2021), is explained by the fact that healthy colonocytes primarily break down butyrate by β-oxidation and use it as a source of energy, but undifferentiated colonocytes, due to the Warburg effect, preferentially use glucose over butyrate for their energetic needs and, as a result, butyrate accumulates and epigenetically induces gene expression changes (Donohoe et al. 2012, Han *et al.* 2018, Jung *et al.* 2021, Salvi and Cowles 2021).

In a study that unveiled fundamental differences in energy metabolism between healthy and malignant colonocytes, Donohoe *et al.* proposed a model to explain the ability of the lumen-to-crypt butyrate gradient to shape gene expression in the colon epithelium in a dose-dependent and cell type-specific manner. At the low concentrations of butyrate (~0.5 mM in mice) that exist near the base of the colonic crypts, most of the butyrate is metabolized and contributes to histone acetylation by a mechanism that involves the formation of acetyl-CoA and histone acetyl transferases, and supports the proliferation of mitotically active colonocytes. Transcriptome profiling revealed that target genes upregulated by this mechanism are enriched for functions related to cell proliferation. Healthy colonocytes preferentially use butyrate as an energy source and metabolize it in the mitochondria by β-oxidation. The higher butyrate concentrations (~5 mM in mice) that exist near the lumen exceed the concentration at which butyrate can be efficiently metabolized, which is approximately 1–2 mM. As a result, butyrate accumulates in the nucleus of colonocytes, acts as an HDAC inhibitor, and decreases cellular proliferation. Transcriptome profiling showed that the targets of this mechanism are enriched for apoptotic genes, supporting the ability of the higher butyrate levels to promote colonocyte apoptosis and exfoliation. In cancerous colonocytes, which due to the Warburg effect rely on glycolysis but metabolize relatively little butyrate, the HDAC inhibition mechanism predominates and leads to decreased cell proliferation and increased apoptosis (Donohoe *et al.* 2012).

In studies that sought to further interrogate the cellular and molecular intricacies of the butyrate paradox, Kaiko et al. showed that in zebrafish, which do not have colonic crypts (Chen *et al.* 2012, Flores *et al.* 2020, Tavakoli *et al.* 2022) but their intestinal stem cells are exposed to the intestinal lumen, and also lack intestinal bacteria that synthesize butyrate, a marked inhibition of intestinal proliferation occurs when the mucosa is exposed to butyrate (Kaiko *et al.* 2016). This suggested that the placement of intestinal stem cells and progenitor cells in colonic crypts (Fig. 2B) protects them from the growth inhibitory effects of butyrate, which could otherwise suppress their division. The metabolization of butyrate into acetyl-CoA in the neighboring colonocytes protects stem cells in the crypts from the effects of butyrate (Kaiko *et al.* 2016), a phenomenon that was relevantly referred to as a *metabolic sinkhole* (Singh *et al.* 2016). Due to the ability to protect stem cells from the anti-proliferative effects of butyrate (Salvi and Cowles 2021), the colonic crypts emerge as their *natural gatekeepers* (Vemula and Jala 2016). In intestinal stem cells and progenitor cells, butyrate increased H3K27 and H3K9 acetylation in a manner dependent, at least in part, on the Forkhead box O3 (Foxo3) transcription factor, which bound the promoters of Cdkn1a, Cdkn1c, and Gadd45b, negative cell cycle regulators that are involved in cell cycle arrest, suppressing cellular proliferation (Kaiko *et al.* 2016). In a human colorectal cancer cell line, butyrate activated pyruvate kinase M2, the pyruvate kinase isoform expressed in cancer cells and stem

cells, and induced a metabolic phenotype that inhibited cellular proliferation (Li *et al*. 2018).

Relative butyrate levels were shown to increase about 4-fold in infants between 6 and 12 months of life (Nilsen *et al*. 2020). Based on the fact that butyrate levels in the intestine increase as the number of stem cells and the intestinal crypt length increase early during postnatal life (Midtvedt and Midtvedt 1992), Gasaly *et al*. hypothesized that colonization with butyrate-producing intestinal microorganisms occurs later during infancy so that butyrate would not interfere with stem cell function and epithelial remodeling during the early postnatal life (Gasaly *et al*. 2021).

Epigenetic effects of SCFAs on cells of the immune system

Accumulating evidence indicates that metabolites derived from the gut microbiota, including SCFAs, modulate gene expression in cells of the innate and adaptive immune system, and some of these effects involve epigenetic mechanisms. *In vitro*, sodium butyrate inhibited the proliferation of mouse malignant mast cells by inducing cell cycle arrest in G_1, increased caspase 3-dependent apoptosis, and increased H3K9 acetylation at the IL-6 and TNF-α promoters, decreasing cytokine production by acting as an HDAC inhibitor (Zhang *et al*. 2016). Butyrate and propionate blocked the formation of dendritic cells from bone marrow stem cells, and this was dependent on their HDAC inhibitory activity (Singh *et al*. 2010). Propionate and butyrate decreased the production of TNF-α, CINC-2$\alpha\beta$ (cytokine-induced neutrophil chemoattractant-2) and nitric oxide (NO) by lipopolysaccharide-stimulated neutrophils and they also inhibited HDAC and the activation of NF-κB, and in a rat model, the administration of tributyrin, a prodrug of butyrate, decreased the migration of neutrophils to the peritoneum after the intraperitoneal administration of glycogen (Vinolo *et al*. 2011).

Butyrate increased the antimicrobial activity of monocytes that were differentiating into macrophages against several Gram-negative and Gram-positive pathogens through a mechanism that involved HDAC3 inhibition. Macrophages differentiated in the presence of butyrate showed a significant decrease in H3K27 trimethylation, which is associated with chromatin repression, and an increase in H3K27 acetylation, which is associated with more open chromatin. These effects were relevant *in vivo*, as shown by the higher antimicrobial activity of colonic macrophages, and a lower dissemination of pathogens from the large intestine to peripheral organs in mice who received butyrate in the drinking water, as compared to control animals (Schulthess *et al*. 2019).

In vitro, butyrate decreased the production of proinflammatory molecules such as NO, IL-6, and IL-12 in bone marrow-derived macrophages and in macrophages from the lamina propria of the colon, and showed similar effects on colon lamina propria macrophages when orally administered to mice, and these effects occurred through the inhibition of HDACs (Chang *et al*. 2014). Butyrate promoted the production of the anti-inflammatory cytokine IL-22 *in vitro* in CD4$^+$ T cells and innate lymphoid cells, and *in vivo* in mice who received it orally in drinking water, by G-protein receptor 41 (GPR41)-mediated signaling and HDAC inhibition. This occurred by its ability to increase the binding of hypoxia-inducible factor 1α (HIF1α) to the hypoxia response element (HRE) of the *Il22* promoter through histone modification. As part of this effect, butyrate increased H3K9 acetylation and suppressed H3K9 trimethylation at the HRE site of the *Il22* promoter (Yang *et al*. 2020). In another study, butyrate modulated the function of Th17 lymphocytes depending on their state of differentiation: in naïve CD4$^+$ T cells undergoing differentiation to Th17 cells, it downregulated the RORγt transcription factor and decreased IL-17 production, but in already differentiated Th17 cells it induced RORγt expression and IL-17 secretion, an effect that was mediated by histone H4 acetylation near the *RORγT* proximal promoter (Sałkowska *et al*. 2017). Butyrate, and to a lesser extent acetate and propionate, decreased the human gut lamina propria CD4$^+$ T cell activation and proliferation *in vitro* by increasing H3K9 acetylation and lowered the production of inflammatory cytokines such as IL-17 and IFNγ (Kibbie *et al*. 2021). Butyrate increased the expression of Treg-associated FoxP3 in a concentration-dependent manner and enhanced the differentiation of T cells into regulatory T (Treg) cells over inflammatory T helper (Th) cells, including Th17 cells (McBride *et al*. 2022). Mice that were fed butyrylated high-amylose maize starch, which was formed by the treatment of starch with butyric anhydride, showed an increased differentiation of Treg cells from the colon lamina propria and in the number of IL-10 producing Treg cells as compared to animals fed a control diet. At least one of the mechanisms explaining this effect involved the epigenetic upregulation of the *Foxp3* gene, as shown by an increased histone H3 acetylation in the promoter and conserved noncoding sequences of the gene (Furusawa *et al*. 2013).

Intestinal SCFAs epigenetically change gene expression at extraintestinal sites

Animal and human studies implicated gut dysbiosis in the development of neuropsychiatric conditions (Kowalski and Mulak 2019, Li et al. 2021, Romano et al. 2021, Chen et al. 2022), and manipulating the gut microbiota decreased neuroinflammation and/or improved certain cognitive or pathological features (Sampson et al. 2016, Bonfili et al. 2021, Qian et al. 2022, Wang et al. 2022), implicating the gut microbiota in the regulation of the gut-brain axis. As part of this connection, microbial metabolites such as SCFAs have received increasing attention (Silva et al. 2020, Begum et al. 2022, O'Riordan et al. 2022).

In 1973, Oldendorf reported that ^{14}C-SCFAs injected in the carotid artery of rats cross the blood-brain barrier (BBB), and the relative order of crossing was butyrate (highest), propionate, and acetate (Oldendorf 1973). This finding, and the bioactive properties of SCFAs in the brain, were subsequently confirmed by other studies, and while initially it was believed that SCFA levels are much lower in the brain than in the plasma, the brain levels of butyrate and propionate are higher than originally thought (Wishart *et al*. 2018, Dalile *et al*. 2019, Silva *et al*. 2020, Wenzel *et al*. 2020, Colombo *et al*. 2021, Fillier *et al*. 2022, Fock and Parnova 2023). SCFAs emerge as a potential link between the gut microbiota and the pathology of several neurodegenerative diseases. In human neuroblastoma-derived and rat mesencephalon-derived cell lines, sodium butyrate partially prevented the apoptotic cell death caused by the mitochondrial toxin 1-methyl-4-phenylpyridinium, and this was accompanied by a significant increase in histone H3 acetylation (Kidd and Schneider 2010). In another study, sodium butyrate increased brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) transcription in primary cortical astrocyte cultures, along with an increase in histone H3 acetylation at the *GDNF* promoter (Wu *et al*. 2008). Butyrate inhibited the aggregation of β-amyloid 1–40 and 1–42 monomers into fibrils *in vitro* by interfering with protein-protein interactions (Ho *et al*. 2018), and showed benefits in several mouse models of Alzheimer's disease (Cao *et*

al. 2018). In a mouse model of early Alzheimer's disease, the oral administration of sodium butyrate decreased β-amyloid levels and improved cognitive memory (Fernando *et al*. 2020), and in a presenilin-1 and presenilin-2 conditional double knockout mouse model it significantly increased neurogenesis in the subgranular zone of the dentate gyrus, restored contextual memory, and reversed the dysregulated histone acetylation in the hippocampus and the cortex (Cao *et al*. 2018). A cross-sectional study of elderly individuals found that brain amyloid deposition and endothelial dysfunction were positively correlated with blood acetate levels and negatively correlated with butyrate levels (Marizzoni *et al*. 2020). In a mouse model of Parkinson's disease, butyrate prevented the DNA damage caused by α-synuclein, possibly by upregulating DNA repair genes, and in cell lines it rescued the decrease in histone H3 acetylation that was mediated by α-synuclein (Paiva *et al*. 2017). In a rat model of 6-hydroxydopamine-inducecd experimental Parkinson's disease, intraperitoneal sodium butyrate attenuated the motor deficits, increased dopamine levels in the striatum, and lowered oxidative stress, along with increasing striatal global histone H3 acetylation levels (Sharma *et al*. 2015).

The microbiota additionally regulates the gut-brain axis through several metabolites that preserve the integrity of the BBB, including SCFAs, by mechanisms that include epigenetic changes (Fock and Parnova 2023). Germ-free mice have an increased BBB permeability starting with the intrauterine life and continuing into adulthood, as compared to pathogen-free mice harboring a normal gut microbiota, significantly lower levels of occludin and claudin-5 in the tight junctions from the frontal cortex, striatum, and hippocampus, and fewer intact tight junctions in the striatum. The colonization of germ-free mice with pathogen-free gut microbiota, or the administration of bacteria making SCFAs, such as *Clostridium tyrobutyricum*, which produces mainly butyrate, or *Bacteroides thetaiotaomicron*, which produces mostly acetate and propionate, decreased the permeability of the BBB, an effect that was also achieved by the administration of sodium butyrate by oral gavage. Sodium butyrate increased the expression of occludin in the frontal cortex and the hippocampus, and monocolonization of germ-free mice with *C. tyrobutyricum*, or the administration of sodium butyrate, increased histone H4 acetylation in extracts from the frontal cortex (Braniste *et al*. 2014).

In vitro, SCFAs downregulated the production of pro-inflammatory molecules by downregulating nuclear factor-κB (NF-κB) (Liu *et al*. 2012), and in a rat model of transient focal cerebral ischemia, valproic acid, an HDAC inhibitor, reduced the degradation of tight junction proteins and the nuclear translocation of NF-κB, effects that were mimicked by sodium butyrate (Wang *et al*. 2011). In a rat model of middle cerebral artery occlusion, the administration of a selective HDAC3 inhibitor early after the occlusion decreased cerebral edema and BBB leakage, and these effects were at least in part mediated by upregulating tight junction proteins and decreasing NF-kB-mediated inflammation (Lu *et al*. 2023). In a mouse model of type 2 diabetes, which showed increased hippocampal and cortical Hdac3 levels and activity, inhibition of Hdac3 significantly upregulated several tight junction and adherens junction proteins and improved BBB permeability. The miR-200a/Keap1/Nrf2 was required for this effect, pointing towards the possibility that the epigenetic modification of Nrf2 could explain the protection that SCFAs confer to the integrity of the BBB (Zhao *et al*. 2019).

Several studies support the benefits of butyrate in ischemic stroke. The first study to show that sodium butyrate causes epigenetically mediated selective gene expression changes in microglia in ischemic stroke was a mouse model of cerebral artery occlusion, which found that intraperitoneally administered sodium butyrate downregulated pro-inflammatory mediators, such as TNF-α and STAT1, and upregulated the anti-inflammatory mediator IL-10, due to its ability to modulate H3K9 acetylation levels (Patnala *et al*. 2017). In a rat model of ischemic stroke, sodium butyrate reduced the size of the injury and suppressed neurological deficits, likely by several mechanisms, including suppression of inflammation, and the benefits appeared to be explained by the HDAC inhibitor-induced apoptosis of microglia and monocytes/macrophages, which decreased neuroinflammation (Kim *et al*. 2007). In another study that investigated a rat model of permanent brain ischemia, the subcutaneous injection of butyrate stimulated neurogenesis in the subventricular zone and hippocampal dentate gyrus, two neurogenic regions of the brain, and this was correlated with increased acetylated histone H3 levels in these regions, and upregulated the levels of BDNF, phospho-CREB, and GFAP in several regions of the brain (Kim *et al*. 2009).

SCFAs can induce epigenetic changes in various immune cells from multiple body compartments (Yip *et al*. 2021). Germ-free mice exhibited structural and functional defects in microglia, and some of the genes that were dysregulated, such as *Hdac1*, *Sirt2*, and *Mll3*, encode well-known epigenetic regulators. These phenotypes were mimicked by the deficiency of the FFAR2 receptor for SCFAs and were reversed by SCFA supplementation (Erny *et al*. 2015). Mice fed with inulin had increased levels of all three SCFAs in the cecum and increased levels of butyric and propionic acid in the hepatic portal vein, and in *ex vivo* experiments, their microglia secreted significantly less tumor necrosis factor α (TNF-α) in the presence of lipopolysaccharide as compared to mice fed a control diet. This suggested that part of the SCFAs generated in the large intestine may regulate microglial activation. *In vitro*, butyrate and acetate inhibited the inflammatory response of microglia stimulated with lipopolysaccharide, most likely through an epigenetic mechanism that involved inhibition of HDAC and NF-κB activity (Caetano-Silva *et al*. 2023).

Propionate and butyrate affected the adhesion of human eosinophils to endothelial cells *in vitro*, impaired their viability, and activated apoptosis, and butyrate impaired their ability to migrate, effects that were accompanied by increased histone H3 acetylation (Theiler *et al*. 2019).When administered in the drinking water or intranasally to mice, butyrate regulated the function of type 2 innate lymphoid cells in the lungs and attenuated airway hyperreactivity and inflammation, effects that occurred through HDAC inhibition and were accompanied by increased histone H3 lysine 9 and 14 acetylation (Thio *et al*. 2018). A high fiber diet or acetate administered to mice protected against allergic airway disease in a manner that required HDAC9 inhibition and was dependent on Treg cells, and maternal high fiber diet or acetate also conferred protection to the offspring when allergic airway disease was induced. These effects were mediated *in utero* and were not dependent on the transfer of microbiota to the fetus. In both adult mice and the offspring, there was an increased acetylation of histone H4 and histone H3K9 at the *Foxp3* promoter, an increased Foxp3 expression in the lungs, and an increase in the number and function of Treg cells in the lungs (Thorburn *et al*. 2015).

SCFAs epigenetically regulate multiple gut-organ axes and various cell types in the body (Fig. 3). A study on mice found that the gut microbiota regulates global histone acetylation and methylation in several host tissues, including colon, liver, and white adipose tissue, in a manner that is shaped by diet, and the oral administration of SCFAs to germ-free animals recapitulated some of the chromatin modification states associated with gut microbiota colonization (Krautkramer *et al*. 2016). In mouse adipocytes, bu-

tyrate and propionate stimulated lipolysis *in vitro*, an effect that was mimicked by the HDAC inhibitor trichostatin A (Rumberger *et al*. 2014), and in rats with type 2 diabetes mellitus fed a high-fat diet and administered streptozotocin, intraperitoneal sodium butyrate significantly reduced plasma glucose, insulin resistance, and liver steatosis, effects that occurred through HDAC inhibition and were accompanied by histone H3 hyperacetylation in liver tissue (Khan and Jena 2016). In another study, the oral administration of sodium butyrate to mice fed a high fat diet alleviated obesity, improved glucose tolerance, restored plasma insulin and leptin levels, and significantly reduced lipid deposition in skeletal muscle. These effects appeared to mainly occur through HDAC inhibition, and H3K9 acetylation was increased at the promoters of *Adipor1* and *Adipor2*, which encode adiponectin receptors, and *Ucp2* (uncoupling protein 2) and *Ucp3* (uncoupling protein 3), which are involved in mitochondrial thermogenesis and β-oxidation (Hong *et al*. 2016).

In rat neonatal cardiomyocytes, butyrate increased histone H3 acetylation as a result of HDAC inhibition and suppressed endothelin-1-induced cardiomyocyte hypertrophy (Umei *et al*. 2020). Sodium butyrate attenuated angiotensin II-induced cardiac hypertrophy in rats and, *in vitro*, this was shown to require the inhibition of the COX2/PGE2 pathway in an HDAC5- and HDAC6-dependent manner (Zhang *et al*. 2019). Butyrate lowered LDL cholesterol levels in HepG2 cells through HDAC inhibition (Bridgeman *et al*. 2022), a significant finding considering that the liver can extract butyrate that is absorbed from the large intestine (Guilloteau *et al*. 2010, Blaak *et al*. 2020). In an observational study of 92 consecutive patients, the levels of propionate and butyrate in blood and fecal samples negatively correlated with the vascular calcification score of the aorta, and sodium propionate administered orally or rectally to rats ameliorated calcium deposition in the ascending aorta and decreased plasma levels of inflammatory cytokines (Yan *et al*. 2022). This is a relevant finding, considering that butyrate conferred atheroprotective functions *in vitro* by inhibiting the proliferation of vascular smooth muscle cells as a result of epigenetic changes in histone and non-histone proteins and through additional mechanisms (Mathew *et al*. 2010, Cantoni *et al*. 2013, Aguilar *et al*. 2014). In a genome-wide association meta-analysis, several single nucleotide polymorphisms at the *HDAC9* locus were associated with the atherosclerotic calcification of the abdominal aorta, an association that is intriguing, considering that mice deficient in Hdac9 exhibited reduced aortic calcification and improved survival, and in human aortic smooth muscle cells, *HDAC9* overexpression increased mRNA levels of *RUNX2*, a master regulator of the osteogenic phenotype, and led to calcification and reduced contractility (Malhotra *et al* . 2019).

In the first study to show that dietary modification of the gut microbiota can prevent experimental acute kidney injury, the administration of a high fiber diet to mice with folic acid nephropathy, or supplementation with acetate, butyrate, or propionate in the drinking water, decreased the expression of several pro-inflammatory cytokines and chemokines and protected against the development of acute and chronic kidney injury. In this study, the high fiber diet or the administration of acetate or propionate in the drinking water significantly downregulated the kidney tissue levels of HDAC4, which has immunomodulatory functions, and HDAC10, which contributes to DNA repair, autophagy, and cancer progression, as compared to controls (Liu *et al*. 2021).

Crotonylation and HDAC-dependent gene expression regulation

Besides acetylation, crotonylation has emerged as a new epigenetic change involved in the communication between the gut microbiota and the host (Tan *et al*. 2011, Fellows and Varga-Weisz 2020). Crotonylation is an evolutionarily conserved histone post-translational modification, present from yeast to humans, which involves the reversible covalent attachment of a crotonyl group to the ε-amino group of the lysine side chain (Liu *et al*. 2018, Wang *et al*. 2021), and was recently also described on serine residues (Liao et al. 2020). Crotonylation was described on histone H1 and all the core histone proteins (Tan *et al*. 2011) as well as on non-histone proteins (Xu *et al*. 2017), and is involved in many cellular functions (Wei *et al*. 2017). X-ray crystallography showed that crotonylation on histone H3 weakens the hydrogen bonds between the histones and DNA and decreases their interaction, opening the chromatin structure (Suzuki *et al*. 2016). HATs have histone crotonyltransferase (HCT) activities, and HDAC1, HDAC2, and HDAC3 are the major histone decrotonylases (Sabari *et al*. 2015, Wei *et al*. 2017, Fellows *et al*. 2018), but no crotonyl-specific writers have yet been identified (Jiang *et al*. 2021) (Fig. 4). In cell-free assays, histone crotonylation catalyzed by the HAT p300 stimulated gene transcription to a greater degree than the one catalyzed by the p300 histone acetylation (Sabari *et al*. 2015). A study of histone crotonylation in several mouse tissues found that the colon and the brain had the highest levels of H3K18 crotonylation, and while several lysine residues were crotonylated in the small intestine, the H3K18 crotonylation mark was the most abundant one. In the colon epithelium, H3K18 crotonylation was associated with transcription start sites. Antibiotic treatment of the mice led to a decrease in the SCFAs in the colon and serum, and a decrease in histone H3K18 and H4K4 crotonylation in the colon. Butyrate promoted histone crotonylation in human colon carcinoma cells and in gut organoids (Fellows *et al*. 2018). Histone crotonylation is linked to cell cycle progression (Fellows *et al*. 2018), it is required for various processes, including spermatogenesis (Liu *et al*. 2017), the renewal of mouse embryonic stem cells (Wei *et al*. 2017), and the regulation of telomeres (Fu *et al*. 2018), and was shown to be dysregulated in several cancer types (Wan *et al*. 2019). In a rat model of neonatal hypoxic-ischemic brain damage, sodium butyrate decreased the damage in the cerebral cortex and the hippocampus, ameliorated behavioral function, and improved H3K9 crotonylation at several neurotrophic genes where it was downregulated during the hypoxic-ischemic encephalopathy, such as *Bdnf*, *Manf*, *Ogdh*, and *Cdnf* (He *et al*. 2022).

Conclusions and Perspectives

During the past several decades, an increasing number of studies have underscored the importance of the gut microbiota in shaping host physiology, and connected intestinal dysbiosis with various diseases that affect organs within and beyond the gastrointestinal tract. Consequently, significant attention was dedicated to identifying the microbial metabolites that orchestrate these connections. SCFAs are emerging as key molecules that explain the ability of the gut microbiota to shape the function of multiple types of eukaryotic cells from different organs and body sites. In addition to their effects on the cells lining the gastrointestinal tract, where their effects depend on their concentration and the cellular state of differentiation, SCFAs modulate gene expression in

cells of the innate and adaptive immune system, adipocytes, and skeletal, cardiac and vascular smooth muscle cells, and shape the function of organs that include the brain, the lungs, and the kidneys. The mechanisms involved in these effects include epigenetic changes, and the ability of SCFAs to increase histone acetylation, and to act as histone deacetylase inhibitors, is emerging as an important topic that will support efforts to better understand physiological processes, interrogate disease pathogenesis, and develop novel biomarkers and therapeutic approaches.

Conflict of interest . None declared.

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