Microbial short chain fatty acids: Effective histone deacetylase inhibitors in immune regulation (Review)

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Abstract. Histone acetylation modification represents a common epigenetic regulatory mechanism, carrying out an indispensable role in cellular gene transcription and function. Histone deacetylases (HDACs) are responsible for regulating gene expression by controlling the deacetylation of histones and non-histone proteins, and can serve as effective targets for participating in immune regulation. Short-chain fatty acids (SCFAs) are important metabolites produced by the gut microbiota that modulate host immunity. SCFAs possess extensive inhibitory activities on class I and II HDACs, as well as acetylation-modifying effects. Based on these, the present review initially introduces the microbial synthesis and intestinal absorption of SCFAs, as well as the classification and function of HDACs. Subsequently, the present review comprehensively summarizes the direct regulatory effects of SCFAs on immune cells through HDAC inhibition, encompassing innate immune cells (macrophages, dendritic cells, neutrophils, mast cells and natural killer cells) as well as T/B lymphocytes. Moreover, the present review further discusses the local intestinal and extra-intestinal (primarily involving the liver, kidney, nerves and blood vessels) protective effects of SCFAs, which are mediated by their HDAC-inhibiting activities. Finally, the present review summarizes the therapeutic potential of SCFAs as effective HDAC inhibitors in ameliorating intestinal and extra-intestinal diseases and discusses the research prospects. The present review aims to elucidate the regulatory effects of SCFAs on host immunity through HDAC inhibition, highlighting their therapeutic potential for human diseases.

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Contents

1. Introduction

Epigenetics constitutes an important part of the immunoregulatory mechanisms within the human body. The posttranslational modification of histones represents a notable epigenetic mechanism that influences DNA structure and function, primarily encompassing mechanisms such as methylation, acetylation, phosphorylation and ubiquitination. Among them, histone acetylation is a commonly and extensively studied epigenetic regulatory mechanism. It carries out a pivotal role in modulating chromatin activity and subsequent gene transcription (1). The process of histone acetylation is reversible and is meticulously regulated by a series of enzymes. For instance, histones undergo acetylation under the catalytic influence of histone acetyltransferases (HATs) families. However, this acetylation can be reversed and removed by histone deacetylases (HDACs), leading to the inhibition of gene transcription. As their name implies, HDACs are responsible for removing acetyl groups from histones, thereby influencing the expression of DNA-encoded genes that are associated with these histone molecules (2). Moreover, an abundance of evidence suggests that HDACs can also deacetylate non-histone proteins, which consequently exerts influence on cellular physiological processes (3). Given their effects on the cellular functions, HDACs carry out a pivotal role in regulating both innate and adaptive immune pathways. Consequently, HDACs are widely recognized as key inflammatory and immune regulators. Numerous HDAC inhibitors (HDACis) have been developed as therapeutic agents, with cancer currently being their main clinical indication. Promising clinical progress is being made regarding their therapeutic effects on inflammatory diseases,

neurodegenerative diseases, HIV infection and other conditions (4,5). As aforementioned, HDAC-mediated deacetylation holds great importance for gene transcriptional activity and can serve as an effective target for regulating the immune response of the body.

The gut microbiota constitutes a highly intricate community of microorganisms that colonize in the human intestinal tract. It facilitates the digestion and metabolism of nutrients, as well as promoting the maintenance of host immune homeostasis. This beneficial effect can be largely attributed to the key molecular signals delivered by a 'healthy' microbiome. These signals can stem from microbial surface antigens or active metabolites, and they hold importance for the proper development and function of the immune system (6,7). A previous study revealed that microbial signals are capable of calibrating the transcriptional programs of host cells through epigenetic modifications, which in turn regulate both innate and adaptive immune responses. Notably, metabolites originating from the microbiota, acting as key epigenetic substrates and enzyme regulators, have the potential to promote crosstalk between the microbiota and the host by inducing histone modifications (8). Short-chain fatty acids (SCFAs) are metabolic products generated by gut microbes and are recognized as pivotal mediators in the interplay between the microbiota and the immune system. Importantly, SCFAs can exert immunomodulatory effects at both local intestinal and systemic levels, primarily relying on evolutionarily conserved processes involving the G protein-coupled receptor (GPCR) signaling and the HDAC inhibition (9). Specifically, SCFAs can function as the HDACi, targeting the epigenome by inducing chromatin remodeling that subsequently influences cellular processes and functions. Typically, the HDAC inhibition targeted by SCFAs fosters a tolerogenic or anti-inflammatory cellular phenotype, which carries out a key role in maintaining immune homeostasis. It is well-established that the anti-inflammatory effects of SCFAs, grounded in HDAC inhibition, encompass not only epithelial cells but also a diverse range of immune cells, including peripheral blood monocytes, neutrophils, dendritic cells (DCs), macrophages and T cells (6,10,11). Collectively, these findings substantiate the key notion that SCFA metabolites can act as epigenetic regulators, thereby enabling the gut microbiota to modulate host immune responses.

In recent years, the multifaceted HDAC inhibition exhibited by SCFAs has been increasingly elucidated. SCFAs not only increase the epithelial barrier function in the gut but also shape the host immune system, thereby promoting both intestinal and systemic immune homeostasis. Given these findings, the present systematic review discusses, at both cellular and systemic levels, the regulatory effects of SCFAs on host immunity mediated by HDAC inhibition. The present review was conducted in accordance with the PRISMA guidelines (12). Comprehensive searches were carried out across Medline (https://www.nlm.nih.gov/medline/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), Web of Science (URL: https://www.webofscience.com/) and other databases (https://www.sciencedirect.com/) from inception until September 30, 2025. The search strategy utilized the full terms 'short-chain fatty acids' (abbreviated as 'SCFAs') and 'histone deacetylases' (abbreviated as 'HDAC'), along with other core terms such as 'acetate', 'propionate', 'butyrate' and 'acetylation'. These were combined with modifiers, including 'gut microbiota', 'immune cells', 'T/B cells', 'immune diseases' and 'anti-bacterial/anti-inflammatory effects', using Boolean operators ('AND', 'OR') to refine the search. Examples of search strings are as follows: ('Short-chain fatty acids' OR 'SCFAs') AND 'gut microbiota', ('short-chain fatty acids' OR 'SCFAs') AND 'histone deacetylases' OR 'HDAC' OR 'acetylation') AND ('anti-bacterial effects' OR 'anti-inflammatory effects') and ('acetate' OR 'propionate' OR 'butyrate') AND ('histone deacetylases' OR 'HDAC' OR 'acetylation') AND ('immune cells' OR 'T/B cells' OR 'immune diseases'). According to these, the present review begins by providing an overview of the microbial production and intestinal absorption of SCFAs, accompanied by a detailed description of the classification and function of HDACs. Furthermore, it offers a comprehensive summary of the direct effects exerted by SCFAs on immune cells (innate immune cells and lymphocytes) through HDAC inhibition, as well as the systemic protective roles they carry out both within and outside the gut. Finally, the present review delves into the therapeutic potential of SCFAs as HDACi in ameliorating various immune-related diseases and discusses the research prospects. The outline of the present review is depicted in Fig. 1.

2. Microbial synthesis and intestinal absorption of SCFAs

Indigestible carbohydrates, such as dietary fibers, serve as the key sources of SCFAs (13). Given that the human gut lacks specific metabolic enzymes, carbohydrates require fermentation by intestinal microorganisms to be hydrolyzed and subsequently converted into SCFAs. The gut microbial population, which ranges from 10^{13} to 10^{14} in number, encodes the vast majority of carbohydrate-active enzymes that complete the metabolic conversion of carbohydrates into SCFAs (13). SCFAs encompass acetate (C2), propionate (C3), butyrate (C4), valerate (C5), caproate (C6), as well as other branched SCFAs such as iso-valeric acid and iso-butyric acid. Notably, acetate, propionate and butyrate constitute the majority (90-95%) of intestinal SCFAs (14). The synthesis of these SCFAs occurs through distinct pathways, yet all can trace their origins back to the common precursor, pyruvate. Pyruvate is generated through the glycolytic pathway of (deoxy-) hexoses and the pentose phosphate pathway, following the microbial hydrolysis of carbohydrates. Gut microbiota can produce acetate by metabolizing pyruvate through either the acetyl-CoA pathway or the Wood-Ljungdahl pathway. The biosynthesis of propionate proceeds via three pathways: The acrylate pathway, the succinate pathway and the propanediol pathway. Butyrate synthesis is facilitated by the key enzymes such as butyrate kinase or butyryl-CoA: Acetate CoA transferase (15,16) (Fig. 2). Acetate serves as the primary net product of the majority of intestinal bacteria, while the synthesis of propionate and butyrate demonstrates distinct, species-specific characteristics. For example, bacteria that generate propionate through the succinate pathway predominantly belong to the phyla *Bacteroidetes* and *Negativicutes* (within the *Firmicutes* phylum) (15). The propanediol pathway, which is responsible for metabolizing deoxy-hexoses such as fucose and rhamnose, is notably more prevalent among members of the

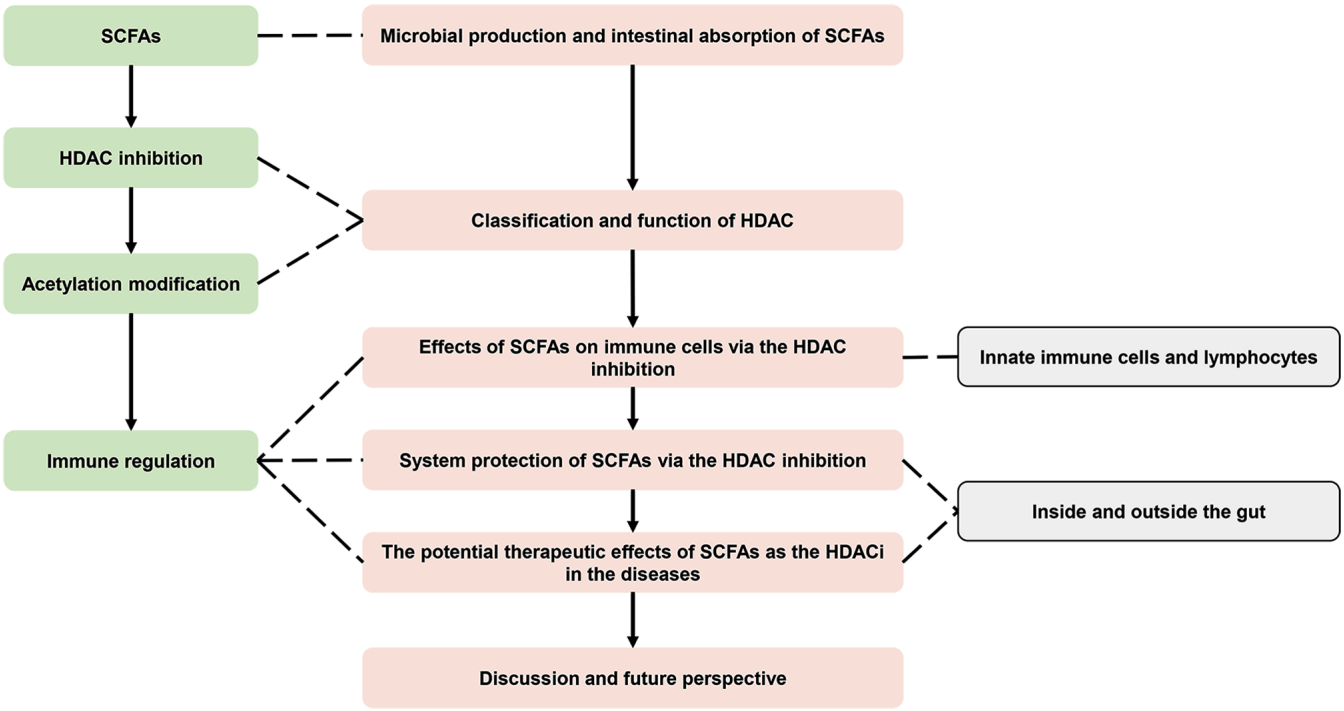

Figure 1. Outline of the present review. Left panel: The major processes that SCFAs mediate the immune regulation via HDAC inhibition. Middle and right panels: The corresponding sections of the present review. SCFAs, short chain fatty acids; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor.

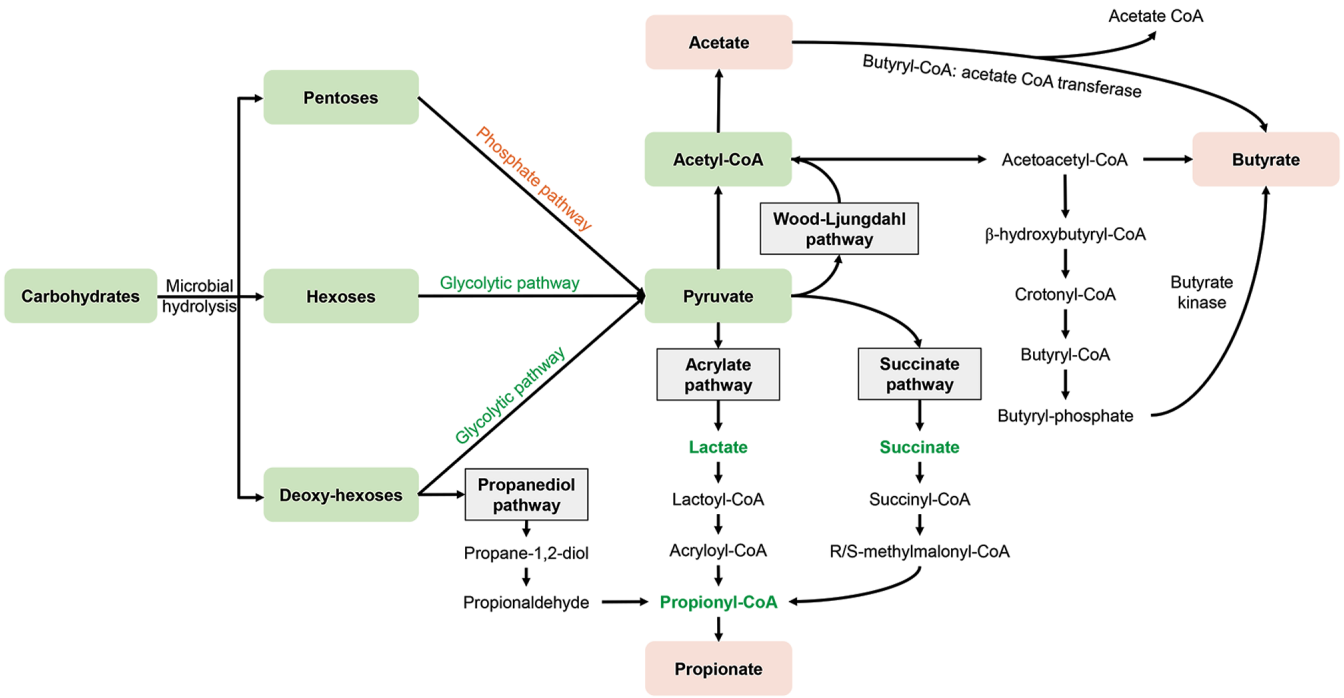

Figure 2. The main pathways by which gut microbiota hydrolyze carbohydrates to synthesize SCFAs. The synthetic routes for the three primary SCFAs-acetate, propionate and butyrate-are listed as follows: i) The Wood-Ljungdahl pathway or acetyl-CoA pathway for acetate synthesis; ii) the acrylate pathway, succinate pathway or propanediol pathway for propionate synthesis; iii) the pathway for butyrate synthesis relying on key enzymes such as butyrate kinase or butyryl-CoA: Acetate CoA transferase.

Lachnospiraceae family. Furthermore, *Coprococcus catus*, a genus within *Lachnospiraceae*, has the ability to increase propionate production via the acrylate pathway (17). Numerous microbes originating from the Firmicutes phylum, including *Faecalibacterium prausnitzii*, *Eubacterium biforme* and *Eubacterium rectale*, are capable of generating butyrate through the butyryl-CoA: Acetate CoA-transferase pathway. By contrast, a limited species of *Firmicutes*, such as *Coprococcus eutactus* and *Subdoligranulum variabile*, employ butyrate kinase for butyrate synthesis (18).

The types and quantities of SCFAs are determined by the factors such as the type of digested substrate and the composition of the microbiota. The uncontroversial finding is that the relative molar ratio of the three main SCFAs-acetate, propionate and butyrate-in the intestine and feces is ~60:20:20% (19). SCFAs generated by microbes can be absorbed by the colonic epithelium and subsequently enter the bloodstream. The main transmembrane transport mechanisms involved in this process include passive diffusion, GPCRs and carrier transportation. Carrier proteins responsible for mediating the epithelial transport of SCFAs comprise H+-coupled monocarboxylate transporters (MCTs) and Na+-coupled sodium-coupled MCTs (SMCTs). The expression of these transporters is modulated by physiological conditions as well as disease states. MCT1 is expressed on the apical membrane, while both MCT1 and MCT4 are expressed on the basolateral membrane of colonic epithelium. These transporters facilitate the influx of SCFAs from the lumen and their efflux into the bloodstream. Additionally, SMCT1 and 2 are exclusively expressed on the apical membrane of colonic epithelial cells, where they mediate the influx of SCFAs from the lumen (20,21). After being absorbed, different SCFAs exhibit distinct distribution patterns within the body. For example, the majority of butyrate serves as the primary energy source for the intestinal mucosal epithelium. Propionate can cross the intestinal epithelium and once absorbed, it undergoes metabolism in the liver and participates in gluconeogenesis. Conversely, acetate can enter the blood to exert its effects in the peripheral circulation and finally be metabolized by peripheral tissues (22).

SCFAs carry out a key role in maintaining host health and influencing disease progression. On the one hand, SCFAs can regulate the expression of relevant genes to protect intestinal epithelial cells (IECs), as well as promote energy homeostasis and host metabolism. SCFAs can also affect the activity and function of innate immune cells, including macrophages, neutrophils and DCs, along with T and B cells. Through these actions, they effectively regulate the immune system and inflammatory responses (23). SCFAs are able to modulate immune and inflammatory responses through two main mechanisms: Activating GPCRs (specifically GPR41, GPR43 and GPR109A) and inhibiting HDACs. However, it is important to emphasize that SCFAs display both pro-inflammatory and anti-inflammatory effects. These dual effects are likely associated with their local concentration and the activity of the receptors they bind to (23,24).

Therefore, SCFAs constitute a vital class of metabolites that are efficiently synthesized by the gut microbiota and subsequently absorbed and utilized by the intestinal tract. The absorbed SCFAs can regulate energy metabolism, as well as immune and inflammatory responses, thus carrying out a pivotal role in maintaining both intestinal and host homeostasis (23,24).

3. Classification and function of HDACs

HDACs exhibit evolutionary conservation in organisms. Based on differences in sequence similarity and enzymatic mechanisms, HDACs can be categorized into four distinct classes: Class I Rpd3-like proteins, including HDAC1, 2, 3 and 8; class II Hda1-like proteins, including HDAC4, 5, 6, 7, 9 and 10; class III Sir2-like proteins, namely sirtuins (SIRTs)1-7, which are structurally distinct from class I or II HDACs; and the unique class IV protein, HDAC11 (Fig. 3) (25,26). Class I HDACs are detectable within the nucleus and demonstrate ubiquitous expression and share sequence similarity with the yeast Rpd3 protein. Conversely, class II HDACs display sequence similarity to the yeast Hda1 protein and carry out tissue-specific roles. Class II HDACs can be further subdivided into class IIa (HDAC4, 5, 7 and 9) and class IIb (HDAC6 and 10). Class IIa HDACs possess relatively low activity and are capable of shuttling between the cytosol and nucleus, whereas class IIb HDACs prefer to act on non-histone proteins and are primarily located in the cytosol (25,26). The class IV protein HDAC11 shares sequence similarity with both class I and II proteins. Furthermore, class I, II and IV all belong to the family of zinc-dependent hydrolases and are collectively known as classical HDACs. By contrast, class III HDACs mainly comprise NAD+-dependent SIRTs1-7, which share sequence similarity with the Sir2 protein (27,28). Except for HDAC11, the physiological roles of other HDACs have been extensively investigated. For example, class I and II HDACs can modulate a variety of cellular functions, including cell proliferation, differentiation and development. They are also implicated in cellular inflammation, immune responses and even cancer progression (29-31). SRITs are associated with a wide range of cellular processes, such as cell survival, cell cycle progression, apoptosis, DNA repair and cellular metabolism. Dysregulation of their enzymatic activity is associated with the pathogenesis of tumors, metabolic disorders, infectious diseases and neurodegenerative conditions (28).

Epigenetic alterations that cause human diseases are emerging as ideal candidates for therapeutic interventions. The deacetylation activity of HDACs, which is intricately associated with various cellular processes, positions them as potentially effective targets for treating human diseases (32). At present, HDACis constitute a category of natural or synthetic compounds that exhibit potent epigenetic regulatory capabilities. These inhibitors can disrupt HDAC function and induce histone acetylation to modulate the expression of genes. Importantly, HDACis exhibit pleiotropic effects at both the cellular and systemic levels and are widely acknowledged for their extensive therapeutic potential in inflammatory diseases and cancer (32). Notably, microbial SCFAs themselves act as the representative HDACis. The extensive HDAC inhibitory activity of SCFAs across various cell types, as well as their crucial roles in immunoregulation, are being systematically investigated. Consequently, the present review focused on and summarized the immunomodulatory effects of SCFAs as HDACis, encompassing their effects from immune cells to the systemic level.

4. Effects of SCFAs on immune cells via HDAC inhibition

SCFAs are vital microbial metabolites that notably influence the intricate interplay between microbes and the host immune system. HDAC inhibition stands as the principal mechanism by which SCFAs regulate gene acetylation modifications in numerous immune cells. Importantly, SCFAs can serve as potent inhibitors of class I/II HDACs (33). In this section, a comprehensive review of the regulatory effects of SCFAs on

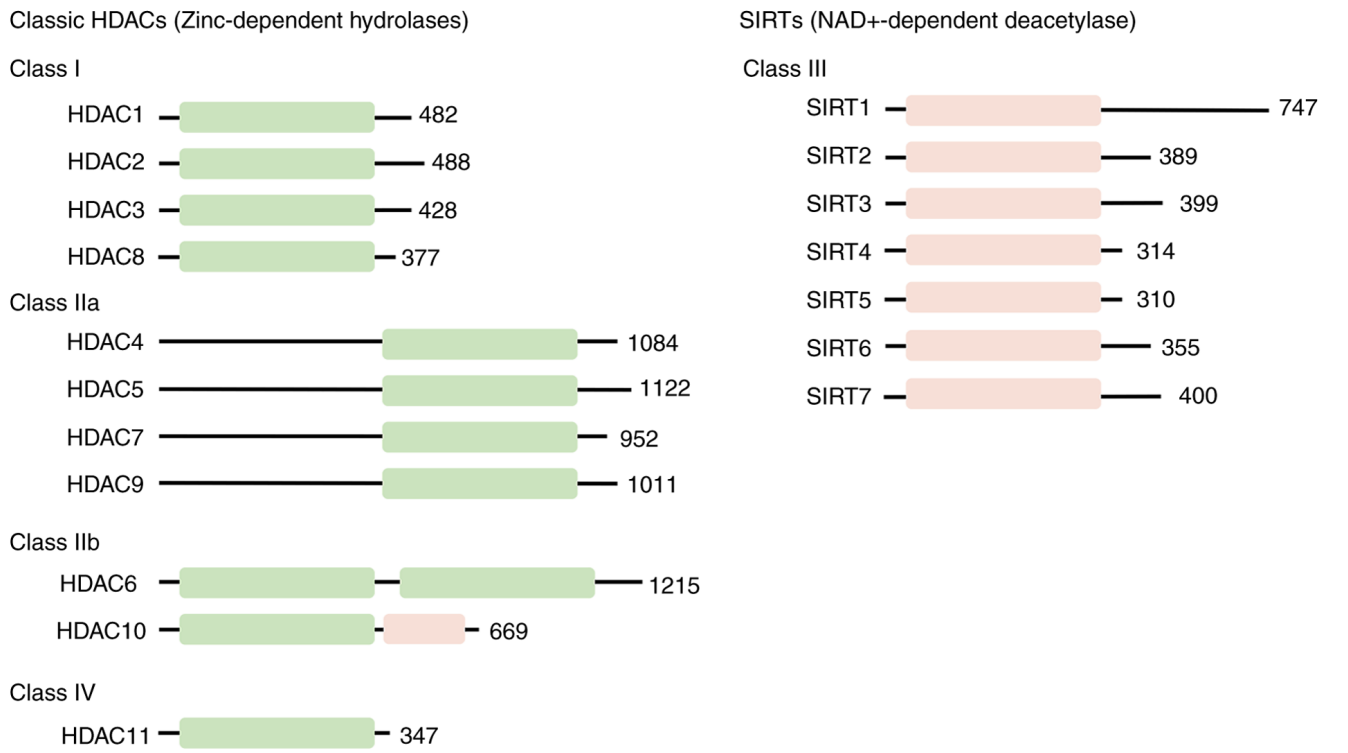

Figure 3. Classification of HDACs. There exist two principal types of HDACs that carry out deacetylation function, namely classic HDACs and SIRTs. Classic HDACs include class I, II and IV HDACs, all of which belong to the family of Zinc-dependent hydrolases. SIRTs, on the other hand, are categorized as class III HDACs and are well-known as NAD+-dependent deacetylases. The enzyme domains are shown in color, and the numbers indicate the counts of amino acids. HDACs, histone deacetylases; SIRTs, sirtuins.

immune cell activities and functions via HDAC inhibition was conducted (Fig. 4). The present review focuses on the inhibitory effects of microbial SCFAs on class I and II HDACs in innate immune cells, as well as their effects on the associated acetylation modifications (such as histones H3 and H4). These immune cells mainly include macrophages, DCs, neutrophils, mast cells (MCs) and natural killer (NK) cells, along with T/B lymphocytes (Fig. 4). This highlights the pivotal regulatory role of SCFAs, which is mediated through HDAC inhibition, at the immune cell level. Thus, this allows for a deeper understanding of the direct contribution of microbial SCFAs to the host immune system from the perspective of epigenetic regulation.

Innate immune cells

Macrophages. Macrophages are extensively distributed throughout the body and carry out a pivotal role in innate immunity, primarily by eliminating bacteria, regulating inflammation and promoting tissue repair (34). In particular, the tissue-resident macrophages exhibit direct activities aimed at eliminating invading bacteria and increasing the defenses of the body. Butyrate emerges as a representative SCFA that modulates the anti-bacterial functions of macrophages. Its underlying mechanism is considered to be associated with HDAC inhibition rather than GPCR activities. For example, SCFAs can enhance the anti-bacterial activity of macrophages differentiated *in vitro*. Notably, 1 mM butyrate exhibits a stronger effect compared with 1 mM propionate, while acetate at the same dosage fails to demonstrate such an activity. The potent anti-bacterial function induced by butyrate stems from glycolysis and mTOR inhibition, which does not require GPCRs but instead depends on HDAC3 inhibition (34). Butyrate (given orally at 150 mM for 21 days or used *in vitro* at 1 mM for 24 h) can enhance the anti-bacterial activity of macrophages by promoting the production of reactive oxygen species (ROS) after infection, markedly improving leptospirosis in hamsters (35). However, acetate and propionate do not have this effect. Mechanistically, butyrate promotes ROS production through MCT-mediated HDAC3 inhibition (35). In addition to phagocytosis and anti-bacterial actions, butyrate at 2 mM for 48 h can also restrict the alternative activation of macrophages induced by IL-4, including inhibiting the activity of regulatory T (Treg) cells and reducing their production of IL-17A. The effects of butyrate can be replicated by HDACis such as trichostatin A (TSA) and valproic acid (VPA) and this replication occurs independently of GPCR signaling (36). Furthermore, the hydroxylated derivative of butyrate, 4-hydroxybutyrate, can also promote the production of antimicrobial peptides (AMPs) in mouse bone marrow-derived macrophages (BMDMs) in an HDAC inhibition-dependent manner, thereby enhancing the endogenous anti-bacterial activity of the immune system. Specifically, butyrate within the concentration range of 0.5-12 mM, when treated for 24 h, can markedly increase the expression levels of cathelicidin LL-37 (37).

The response of activated macrophages to inflammation is determined by distinct cellular subsets: The pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype. M1 macrophages are induced by inflammatory stimuli such as IFN-γ and lipopolysaccharide (LPS) and they participate in

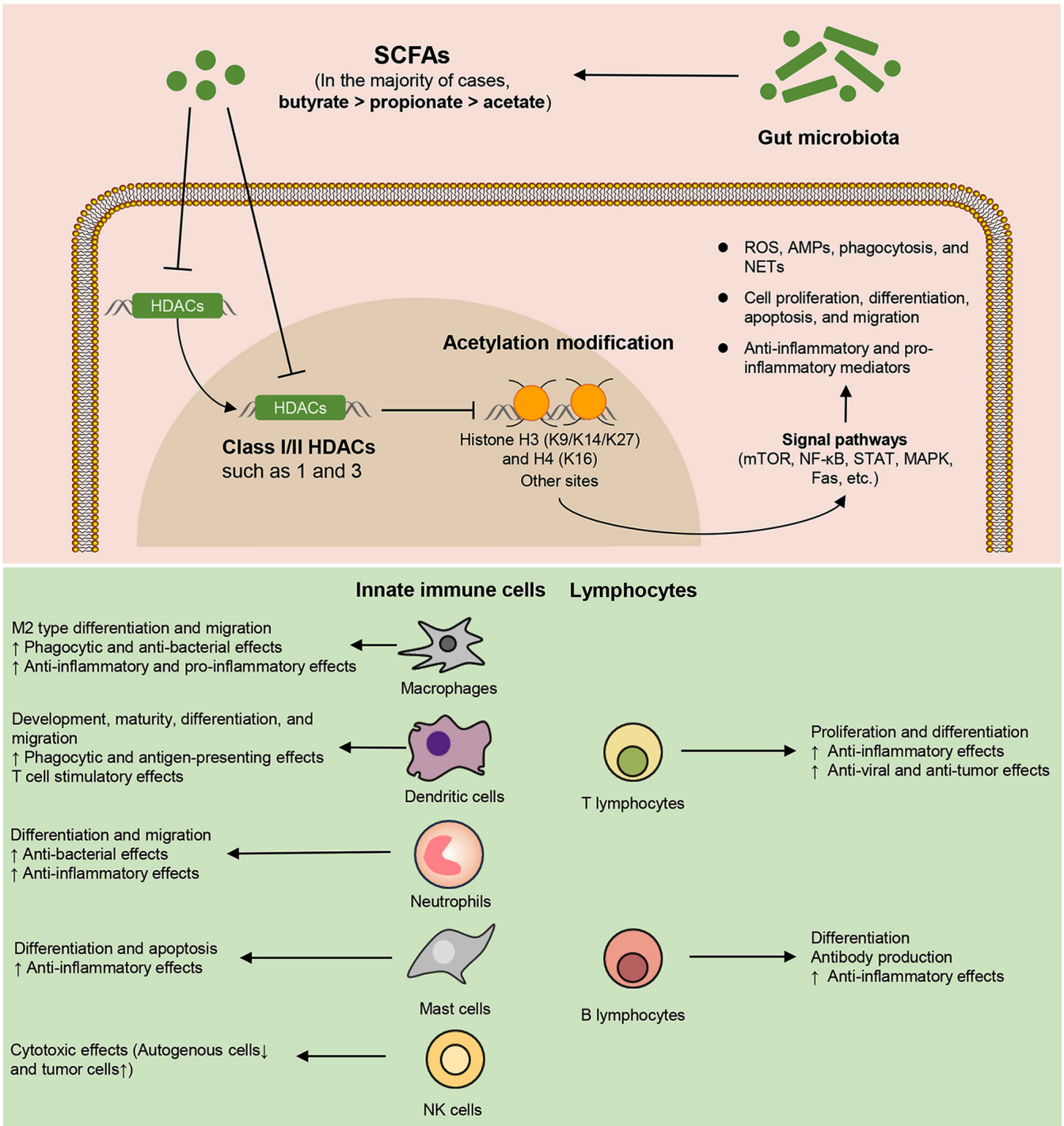

Figure 4. Regulatory effects of microbial SCFAs on immune cell activities and function via HDAC inhibition. SCFAs, primarily consisting of acetate, propionate and butyrate, are capable of promoting acetylation modifications at histones H3 (K9/K14/K27), H4 (K16) and other sites by inhibiting class I/II HDACs. In the majority of cases, the intensity of HDAC inhibition by SCFAs is in the order of butyrate > propionate > acetate. The HDACi effect of SCFAs enables them to modulate the expression of various genes and signaling pathways, ultimately influencing the activities and functions of immune cells. SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; ROS, reactive oxygen species; AMPs, antimicrobial peptides; NETs, neutrophil extracellular traps; M2, macrophage subset 2.

inflammatory and immune responses by secreting pro-inflammatory cytokines and presenting antigens. M2 macrophages, on the other hand, can be activated by cytokines such as IL4 and IL13, and mainly secrete anti-inflammatory cytokines such as IL-10 and TGF-β, carrying out a key role in inflammation resolution and immune modulation (38). In the majority of cases, SCFAs, primarily butyrate, can attenuate the release of pro-inflammatory mediators from activated macrophages through inhibition of HDAC, thus exerting anti-inflammatory effects. For instance, when compared with acetate and propionate, butyrate at 1 mM for 24 h demonstrates a more potent reduction in the levels of pro-inflammatory mediators including NO, IL-6 and IL-12p40 released by LPS-induced BMDMs. It also inhibits the transcription of IL-6, Nos2, IL-12a and IL-12b

in colonic lamina propria (LP) macrophages both *in vitro* and *in vivo*, thereby producing anti-inflammatory effects. The anti-inflammatory effects of butyrate are independent of GPCRs, and instead increase the acetylation levels of histone 3 lysine 9 (H3K9) at the promoter regions of IL-6, Nos2 and IL-12b in cells via HDAC inhibition (39). In *staphylococcal* lipoprotein (Sa.LPP)-induced macrophage inflammation, butyrate and propionate (but not acetate) at 3 mM for 21 h can markedly suppress the NF-κB, IFN-β/STAT1 and HDAC pathways, leading to a reduction in cellular NO release. Similarly, butyrate exerts a stronger effect when compared with propionate in inducing H3K9 acetylation. Additionally, the HDAC inhibitor TSA also decreases NO production induced by Sa.LPP. These findings imply that HDAC inhibition, rather than GPCR signaling, serves as the key molecular mechanism by which butyrate and propionate inhibit NO release from macrophages induced by Sa.LPP (40). Furthermore, butyrate can also inhibit inflammatory responses by regulating other macrophage activities, with its underlying mechanisms being associated with HDAC inhibition (41,42). For instance, macrophage migration is associated with tissue inflammation and immune responses. Treatment with 2 mM butyrate for 1 h can inhibit the migratory activity of RAW264.7 cells and rat peritoneal macrophages triggered by LPS. This effect is mediated by inhibiting the activities of iNOS, steroid receptor coactivator and focal adhesion kinase, similar to the effects of the HDACi TSA (41). In addition to restricting inflammatory macrophages, butyrate exerts anti-inflammatory effects by promoting the polarization of M2 macrophages, both *in vitro* at a concentration of 50 μg/ml for 24 h and *in vivo* at 150 mM for 11 days. Furthermore, it enhances the migratory and wound-healing capabilities of M2-BMDMs. Butyrate primarily enhances the STAT6 signaling pathway through its HDAC inhibitory activity, which involves HDAC1 inhibition and H3K9 acetylation. This action facilitates polarization of BMDMs toward the anti-inflammatory M2 phenotype, thereby alleviating inflammatory bowel disease (IBD) (42). Collectively, the evidence underscores the anti-inflammatory activities of SCFAs, especially butyrate, in macrophages through HDAC inhibition. These activities include inhibiting the release of inflammatory mediators, regulating cell migration and promoting M2-type cell polarization. Such mechanisms hold therapeutic potential for treating inflammatory diseases.

SCFAs exhibit anti-inflammatory properties under homeostatic conditions, whereas they can trigger pro-inflammatory programs in the presence of pathogen- and danger-associated molecular patterns. For example, butyrate and propionate has been have been shown to activate the NLRP3 inflammasome and subsequent IL-1β release in LPS-induced macrophages through HDAC inhibition. Butyrate, at a concentration of 1 mM, can notably promote IL-1β release and at 4 mM, it can induce the maximal release of IL-1β starting from 6 h of stimulation. Mechanistically, the inhibitory effect of butyrate on HDAC promotes the acetylation of H3K27, blocks the transcription of FLICE-like inhibitory protein and IL-10, thereby activating the NLRP3 inflammasome without inducing pyroptosis (43). Park *et al* (44) demonstrated that sodium butyrate is capable of upregulating the gene expression of COX-2 in RAW264.7 macrophages that are stimulated by LPS. This upregulation occurs via MAPK-dependent increases in the phosphorylation and acetylation of histone H3 at the COX-2 promoter region. COX-2 is a pivotal enzyme implicated in inflammatory responses and is rapidly activated in macrophages induced by LPS. When 5 mM butyrate is co-administered with 10 ng/ml LPS, it elicits the most notable induction of COX-2 promoter activity. By contrast, butyrate at this concentration alone exerts no discernible effect on the promoter activity of COX-2. These research findings collectively imply that SCFAs do not invariably exert anti-inflammatory effects.

DCs. DCs serve as professional phagocytes and antigen-presenting cells, carrying out a pivotal role in initiating T-cell activation and adaptive immune responses. DCs mainly comprise two major types, namely immature DCs (iDCs) and mature DCs (mDCs). iDCs can capture antigens and, upon immune stimulation, transform into mDCs, thereby activating their antigen-presentation and T-cell stimulation functions (45). SCFAs are involved in regulating the development, maturation, differentiation, migration and antigen-presentation functions of DCs. Research suggests that some of these regulatory mechanisms are associated with HDAC inhibition. For example, the SCFAs butyrate and propionate both at 0.5 mM for 6 days can inhibit the development of DCs from bone marrow precursor cells induced by granulocyte-macrophage colony-stimulating factor (GM-CSF), while having no impact on granulocyte development. Mechanistically, these SCFAs are transported into cells via the transporter (Slc5a8) and inhibit the expression of PU.1 and RelB through their ability to inhibit HDAC (histone H4 acetylation). Acetate is also a substrate for Slc5a8, but it is not an HDACi and does not influence DC development. This suggests that HDAC inhibition carries out a vital role in DC development (46).

The SCFA butyrate can induce DCs to remain in an immature state and impede their maturation. Research has revealed that butyrate at 1 mM for 24 h can markedly downregulate the expression of surface markers on mDCs. Additionally, it enhances the intracellular endocytic capacity of these cells, diminishes their T-cell stimulatory ability, promotes the production of IL-10 and inhibits the production of IL-12 and IFN-γ. These findings collectively underscore the specific immunosuppressive characteristics of butyrate (47). However, the regulatory effect of butyrate on the phenotypic differentiation of certain DCs may not always be associated with HDAC inhibition. For instance, butyrate, when applied at a concentration of 200 μM for 5 d, does not hinder DC differentiation induced by IL-4 and GM-CSF, whereas it suppresses the acquisition of CD1a that is triggered by cytokine and TLR2 agonist stimulation. Nevertheless, this regulatory effect on CD1a acquisition is not closely associated with the HDAC inhibitory activity of butyrate (48). Upon activation, iDCs transform into mDCs, which can migrate to secondary lymphoid organs and initiate cellular immunity. However, butyrate (200 nM; 24 h) and other HDACi, including TSA and scriptaid, demonstrate effective inhibitory effects on the migration of iDCs stimulated by macrophage inflammatory protein-1α, as well as on the chemotaxis of mDCs. The actions of these HDACi involve a reduction in the surface expression of C-C chemokine receptor type 1 on iDCs and C-X-C chemokine receptor type 4 on mDCs. Additionally, they inhibit the phosphorylation of MAPKs, specifically p38, ERK1/2 and JNK (49,50). The uptake of foreign antigens by DCs and their

subsequent presentation to T cells can be affected by their dendritic activity. A study has revealed that SCFAs, such as butyric acid (1 mM) and valeric acid (10 mM) applied for 24 h, can promote dendritic elongation by inhibiting HDACs rather than relying on GPCRs, activating the SFK/PI3K/Rho signaling pathway and inducing actin polymerization. These effects ultimately lead to an enhanced capacity for antigen uptake and presentation in DCs. Notably, the HDACi TSA also replicates the dendrite-promoting effects of SCFAs (51).

DCs carry out a pivotal role in activating T-cell immune responses due to their remarkable capacity for antigen uptake. Among the SCFAs, butyrate stands out as a representative HDACi that can influence the regulation of DC functions in T-cell proliferation and differentiation (52-54). In the majority of cases, butyrate exhibits immunosuppressive properties in T-cell responses stimulated by DCs. For example, butyrate can alter the developmental trajectory of conventional DCs (cDCs). When administered at 0.5 mM for 4 days, butyrate selectively inhibits the cDC2 lineage and their ability to drive CD4+ T cell proliferation. However, it promotes an increase in the differentiation of Foxp3+ Treg cells, thereby contributing to the intestinal tissue homeostasis. These effects of butyrate are independent of GPCR activity and are instead attributed to the inhibition of HDAC3 (52). Butyrate at 2 mM for 48 h has the ability to induce the production of retinaldehyde dehydrogenase 1 (RALDH1), an enzyme that is responsible for retinoic acid synthesis in DCs. Consequently, it inhibits the maturation and metabolic reprogramming of LPS-induced human monocyte-derived DCs and promotes their polarization towards IL-10-producing type 1 Treg cells. The effects of butyrate rely on RALDH activity, which is driven by the combined action of HDAC inhibition and GPR109A signaling, thereby inducing a tolerogenic DC phenotype (53). Additionally, butyrate promotes the production of the pro-inflammatory cytokine IL-17 by T cells, an effect that is associated with the release of cytokine IL-23 by activated DCs. Berndt *et al* (54) by using LPS to induce mouse bone marrow-derived DCs, discovered that 1 mM butyrate for 18 h could considerably inhibit LPS-induced DC maturation and downregulate IL-12 production, while concurrently increasing IL-23 production. The upregulation of the mRNA subunit IL-23p19 at the pre-translational level is consistent with the effect of HDACi on epigenetic modifications of gene expression. The researchers observed that butyrate treatment increased the production of IL-17 and IL-10 by T cells co-cultured with activated DCs, but had no such effect on IFN-γ, IL-4 or IL-13. The *in vivo* therapeutic efficacy of butyrate is dependent on the route of administration. Specifically, oral administration exacerbates colitis, whereas systemic administration improves it. These findings collectively suggest that butyrate induces the production of DC IL-23 and the T-cell pro-inflammatory cytokine IL-17, thereby modulating chemically induced colitis (54).

Neutrophils. Neutrophils represent a key type of immune cell that defends against various pathogens, with their anti-bacterial mechanism of releasing neutrophil extracellular traps (NETs). Research has revealed that SCFAs at physiological concentrations can regulate NET formation in neutrophils. For instance, SCFAs (acetate, propionate and butyrate) at the colonic concentrations are capable of inducing NET formation in neutrophils *in vitro*. When tested at concentrations of SCFAs present in human peripheral blood, only acetate at concentrations of 100 μM (fasting) and 700 μM (postprandial) can considerably induce NET formation. This effect of SCFAs is partially mediated by FFA2R/GPR43 (55). Furthermore, the mechanism by which acetate acting as a HDACi to regulate NET release has also been revealed (56). For example, acetate (at a concentration of 10 mM for 24 h) can considerably enhance the acetylation of histone Ace-H3, H3K9ace and H3K14ace, thereby promoting NETosis in neutrophil-like HL-60 cells, which is a specific form of cell death in which neutrophils release NETs (56).

The accumulation and activation of neutrophils at inflamed sites are associated with the mechanisms of tissue inflammation. The SCFAs, primarily butyrate, exert notable anti-inflammatory effects on activated neutrophils, and this mechanism is associated with HDAC inhibition (57-60). For instance, 1.6 mM butyrate can markedly reduce the production of pro-inflammatory mediators, namely TNF-α, CINC-2αβ and NO, in both *in vitro* and *ex-vivo* neutrophils stimulated by LPS. Notably, propionate exhibits a relatively weaker effect compared with butyrate. It can exert notable inhibitory effects on the release of pro-inflammatory mediators from neutrophils when its concentration reaches 12 mM. Their anti-inflammatory properties are associated with the inhibition of HDAC activity and NF-κB activation (57). Furthermore, the anti-inflammatory effects of butyrate on peripheral neutrophils have been well-validated in both intestinal inflammation models and patients with enteritis. For example, oral administration of 200 mM butyrate can markedly alleviate dextran sodium sulfate (DSS)-induced colitis in mice by inhibiting the neutrophil-derived production of pro-inflammatory cytokines, chemokines, calprotectins and NET formation. In addition, 0.5 mM butyrate can suppress the migration and NET formation of neutrophils isolated from patients with IBD, which encompasses Crohn's disease and ulcerative colitis. Mechanistically, the influence of butyrate on the production of pro-inflammatory mediators is mediated in an HDACi-dependent manner rather than through GPCR signaling (58). In general, a reduction in neutrophil apoptosis is associated with persistent inflammation and may trigger local and systemic inflammatory responses. Consequently, regulating neutrophil apoptosis is a key event for resolving inflammation. Additionally, the HDACi SCFAs may be important microbial metabolites for regulating neutrophil apoptosis. For example, butyrate and propionate, each at 4 mM for 20 h, can notably induce apoptosis in both inactivated and TNF-α/LPS-activated neutrophils. Their mechanisms are independent of GPCRs and MAPKs. Their mechanisms may be related to their HDAC inhibitory activity, which promotes the acetylation of histone H3 and controls the mRNA expression of associated apoptotic protein a1 (59). Butyrate can induce a reduction in the proliferation and an elevation in the apoptosis of CD34+ progenitor cells, and quantitatively and qualitatively impair terminal neutrophil differentiation. This effect of butyrate is accompanied by the increased acetylation of histones 3 and 4, specifically at the H3K9 and H4K16 sites. This observation is consistent with the action exhibited by the HDACi, VPA (60). Taken together, all the findings suggest that butyrate can act as a potent HDACi to suppress neutrophil function and promote its apoptosis, ultimately leading to an effective suppression of tissue inflammation caused by neutrophils.

MCs. Activation of MCs carries out a pivotal role in inflammation and allergic reactions. SCFAs, owing to their HDACi activity, can effectively suppress the activity and function of MCs. Among SCFAs, butyrate and propionate, rather than acetate, inhibit the activation of primary human or mouse MCs via both IgE- and non-IgE-mediated degranulation in a concentration-dependent manner. These effects are associated with HDAC inhibition and are independent of the stimulation of SCFA receptors GPR41, GPR43 or peroxisome proliferator-activated receptor. Epigenomic analysis reveals that 5 mM butyrate not only triggers a redistribution of global H3K27 acetylation levels, but also induces a notable reduction in acetylation at the promoter regions of genes including the tyrosine kinases BTK, SYK and LAT. These kinases are key transducers in the FcεRI signaling pathway that mediates MC activation (61). Additionally, the HDACi butyrate can inhibit the proliferation and induce apoptosis in P815 mastocytoma cells. It also suppresses FcεRI-dependent cytokine production in murine primary bone marrow-derived mast cells (BMMCs). Mechanistically, butyrate at 2 mM for 12 h notably enhances H3K9 acetylation in both P815 and BMMCs, while reducing the FcεRI-dependent mRNA expression of TNF-α and IL-6 in BMMCs. This effect is similarly observed with TSA, a well-known HDACi (62). A study conducted by Gudneppanavar *et al* (62) found that butyrate (5 mM, 24 h) can act as an HDACi to downregulate the growth factor stem cell factor (SCF) receptor KIT and its associated phosphorylation, thereby notably attenuating SCF-mediated proliferation and pro-inflammatory cytokine secretion in BMMCs. Mechanistically, butyrate primarily affects MC function through the inhibition of HDAC1/3. These findings suggest that butyrate can weaken MC function and its inflammatory response by epigenetically modifying histones and downregulating the SCF/KIT/p38/Erk signaling axis (63). Similarly, the proliferative activities of three transformed human MC lines-HMC-1.1, HMC-1.2 and LAD2-are also sensitive to the inhibitory effects of the HDACi butyrate. Butyrate (0-1,000 μM) considerably reduces the expression of c-KIT mRNA and KIT protein in these three cell lines in a dose-dependent manner. The effects of butyrate are associated with cell cycle arrest and a moderate increase in histamine content, tryptase expression and granularity (64).

NK cells. NK cells are of importance in anti-viral defense, anti-tumor responses and immune regulation. They are capable of directly eliminating virus-infected cells and cancer cells, as well as regulating the activities of other immune cells through cytokine secretion. The SCFA butyrate (250 μM, 24 h) can inhibit HDAC activity on human NK cells and influence the epigenetic landscape, phenotype and regulatory functions of NK cells. Specifically, butyrate induces the generation of CD69+ NK cells while simultaneously reducing the proportion of $CD56^{bright}$ NK cells. The inhibition of $CD56^{bright}$ NK cells by butyrate can weaken the attack of NK cells on autologous CD4+ T cells (65). In addition, similar to other HDACi, butyrate (5 mM) can enhance the sensitivity of DAOY and PC3 tumor cells to the cytotoxic effects of IL-2-activated peripheral blood mononuclear cells (PBMCs). NK cells serve as the primary effector cells involved in the lysis of tumor cells. Butyrate also increases the tumor surface expression of ligands for activating NK receptors, namely NKG2D and DNAM-1. As a result, it enhances the susceptibility of tumor cells to the cytotoxic effects of NK cells (66).

Lymphocytes

T lymphocytes. T lymphocytes are the primary effector cells in cellular immunity, mediating inflammatory and immune responses through the production of various cytokines. There is a wide variety of T cells, including CD4+ T cells, CD8+ T cells, γδ T cells and innate lymphoid cells (ILCs). CD4+ T cells are further subdivided into subsets such as Th1, Th2, Th17 and Treg (67). Under physiological conditions, SCFAs have a regulatory role in inhibiting T cell activation, thereby mitigating tissue inflammatory responses. For instance, within intestinal tissues, butyrate (0.0625-0.5 mM) for 4 days is more effective than other SCFAs in reducing the activity of *in vitro* human LP CD4+ T cells and the production of inflammatory cytokines such as IFN-γ and IL-17. The anti-inflammatory effects of butyrate are mediated by both histone acetylation and GPR43 signaling (68). Additionally, butyrate (used *in vivo* at 200 mM or *in vitro* at 0.5 mM) has a broad stimulatory effect on IL-22 production by CD4+ T cells and ILCs in mouse spleens, mesenteric lymph nodes, LP and human peripheral blood. The anti-inflammatory effect of butyrate resulting from this is associated with GPR41 and HDAC inhibition (69). Similar to other HDACi, butyrate (1.1 mM) can induce T cell anergy, a state of antigen-specific proliferative unresponsiveness in CD4+ T cells exposed to antigen. The effect of butyrate in inducing proliferative unresponsiveness in Th1 cells does not rely on general histone hyperacetylation but rather on the secondary effect of histone acetylation, namely the upregulation of p21(Cip1) (70). Furthermore, the anti-inflammatory effects of butyrate include inhibiting IFN-γ-mediated inflammation in colonic epithelial cells and inducing T cell apoptosis to eliminate inflammatory sources. Mechanistic analysis indicated that high concentrations of butyrate (>3 mM) inhibit the activation and proliferation of murine splenic CD4+ and CD8+ T cells *in vitro* and suppresses IFN-γ-induced STAT1 activation and iNOS upregulation in human colonic epithelial cells. Importantly, butyrate can induce hyperacetylation of the Fas promoter and upregulation of Fas by inhibiting HDAC1 activity, thereby inducing apoptosis in CD4+ and CD8+ T cells. This leads to the inhibition of T cell activation and the elimination of the inflammatory source in the colon (71).

However, SCFAs also possess a regulatory role in enhancing the T cell immune activity, particularly in cellular immunity against tumors and viruses. Research has revealed that a relatively high concentration of butyrate (1 mM) can maintain or even increase the ability of T cell receptor (TCR)-transduced CD4+ and CD8+ T cells to release cytokines in response to antigens. Mechanistically, HDAC inhibition by butyrate can enhance the transgenic expression of T cells *in vitro* and their anti-tumor function. This indicates that the HDACi butyrate can augment the tumor-responsive effect of functionally TCR-transduced T cells (72). SCFAs, specifically butyrate and pentanoate, can enhance the anti-tumor activity of two CD8+ T cell subsets, cytotoxic T lymphocytes and chimeric antigen receptor T cells, through metabolic and epigenetic reprogramming. In particular, they can promote the function of mTOR as a central cellular metabolic sensor and inhibit class I HDAC activity. Consequently, these CD8+ T cells

exhibit increased production of effector molecules such as CD25, IFN-γ and TNF-α (73). In addition, 1 mM butyrate can also promote the production of granzyme B and IFN-γ in Tc17 cells, a subset of CD8+ T cells. The increased IFN-γ expression induced by butyrate is mediated through its HDAC inhibitory activity rather than through GPR41 and GPR43 signaling pathways. Moreover, a relatively high concentration of acetate (25 mM) can also increase the production of IFN-γ in CD8+ T lymphocytes, but its underlying mechanism relies on cellular metabolism and mTOR activity (74). Acetate also has a regulatory role in increasing the susceptibility of T cells to HIV-1. Alterations in the fecal microbiota and intestinal epithelial damage associated with HIV-1 infection are likely to causing microbial translocation, thereby exacerbating disease progression and virus-related comorbidities. Notably, the physiological concentration of acetate, that is 20 mM, is capable of enhancing viral production in primary human CD4+ T cells. It also promotes the integration of HIV-1 DNA into the host genome by impairing class I/II HDAC activity. This suggests that acetate can increase the susceptibility of CD4+ T cells to productive HIV-1 infection and may influence the progression of HIV-1-mediated diseases (75). These findings indicate that SCFAs acting as HDACi may hold importance for adoptive immunotherapy against cancer and anti-viral immunity.

Depending on distinct cytokine environments, SCFAs can regulate the differentiation process of naïve T cells into effector cells and Treg cells. For instance, acetate (10 mM), propionate (1 mM) and butyrate (0.5 mM) can induce the differentiation of naïve T cells into Th1 and Th17 cells under polarizing conditions: Th17 (IL-1β, IL-6, IL-21, IL-23, TGF-β1, anti-IL-4 and anti-IFN-γ) or Th1 (IL-12, IL-2 and anti-IL-4). They can also induce the generation of Treg cells such as IL-10+ T cells and Foxp3+ T cells. This effect of SCFAs on T cell differentiation is independent of GPCR receptor signals (GPR41 or GPR43) but depends on HDAC inhibitory activity. Specifically, the inhibition of HDAC by SCFAs increases the acetylation of p70 S6 kinase (P70S6K) and the phosphorylation of rS6, which subsequently drives T cell differentiation through the mTOR pathway to promote either immunity or immune tolerance (76). However, SCFAs are also capable of exerting distinct regulatory effects on T cell differentiation. A study conducted by Chen *et al* (77) revealed that 0.5 mM butyrate can promote the expression of IFN-γ and T-bet to facilitate Th1 cell differentiation while inhibiting the expression of IL-17, Rorα and Rorγt to suppress Th17 cell differentiation. Notably, under both Th1 and Th17 conditions, butyrate can promote the production of IL-10. This, in consequence, diminishes the capacity of T cells to induce colitis, and this effect partially depends on the role of Blimp1. Mechanistically, butyrate promotes Th1 differentiation (but not Th17) by inhibiting HDACs, and this effect is independent of GPR43 signaling. Kespohl *et al* (78) discovered that butyrate at low concentrations (0.1-0.5 mM) can promote the differentiation of Foxp3+ Tregs under TGF-β1 conditions. By contrast, when the concentration reaches 1 mM, butyrate induces the expression of Th1-associated genes, namely T-bet and IFN-γ, in T cells. These dual effects are mediated by the SCFA-induced HDAC inhibition (H3 acetylation) and are independent of the FFA2/GPR43 and FFA3/GPR41 receptors, as well as the Slc5a8 transporter of SCFAs. Additionally, butyrate elevates the expression levels of T-bet and IFN-γ in the colon, exacerbating acute colitis in germ-free (GF) mice. These findings suggest that butyrate requires TGF-β1 to mediate the differentiation of anti-inflammatory Foxp3+ Tregs and can promote inflammatory Th1-related factors at high concentrations, with both effects being associated with HDAC inhibition (78).

Among these T cell subsets, the balance between Th17 and Treg cells is a key factor in determining tissue immune homeostasis and can be regulated by SCFAs (79). Studies (80,81) have revealed that butyrate produced by *Faecalibacterium prausnitzii*, rather than other metabolites, can ameliorate colitis in a DSS-induced mouse model. Mechanistically, butyrate (used *in vitro* at 0.62 mM or *in vivo* at 100 mg/kg) inhibits HDAC3 and c-Myc-related metabolism in T cells, reducing Th17 differentiation. It also promotes the expression of Foxp3 by inhibiting HDAC1 and blocks the IL-6/STAT3/IL-17 downstream pathway. Through these mechanisms, butyrate helps maintain Th17/Treg balance in the gut and exerts potent anti-inflammatory effect (80,81). Butyrate at 1 mM for 5 days is also capable of mediating the K16 acetylation of histone H4, thus upregulating RorγT expression in differentiated Th17 cells while downregulating it in CD4+ T cells under Th17 differentiation conditions. This indicates that butyrate can primarily participate in the epigenetic regulation of RorγT in Th17 cells through HDAC inhibition and is related to specific stages of T cell differentiation (82). More importantly, microbiota-derived butyrate can also promote the gene expression and protein acetylation of Foxp3 to facilitate the differentiation of peripheral Treg cells. Butyrate (500 μM) exerts additional regulatory effects by reducing the expression of pro-inflammatory cytokines in DCs. It achieves this through the acetylation of histone H3, which indirectly promotes the induction of Treg cells. Similarly, propionate exerts HDAC inhibitory activity, enabling it to promote the differentiation of peripheral Treg cells. By contrast, acetate does not possess this activity (83). The aforementioned findings demonstrate that SCFAs can regulate the differentiation and function of T cell subsets based on their HDAC inhibitory activity.

B lymphocytes. SCFAs have the capacity to modulate B cell differentiation, antibody responses and antibody-driven autoimmunity. Notably, propionate and butyrate, primarily at low doses (30 and 20 mM, respectively), can affect B cell function by moderately enhancing class-switch DNA recombination (CSR). However, at higher doses (propionate, 150 mM and butyrate, 140 mM), they lead to a reduction in the expression of activation-induced cytidine deaminase (AID) and Blimp1, as well as a decrease in CSR, somatic hypermutation and plasma cell (PC) differentiation. These effects stem from the direct regulatory role of SCFAs as the HDACi on the intrinsic epigenetic of B cells (84). For instance, by exerting HDAC inhibitory activity, SCFAs upregulate microRNAs that specifically target Aicda and Prdm1 mRNAs. As a result, the expression levels of Aicda and Prdm1 (which respectively encode AID and Blimp1) within B cells are diminished (84).

Furthermore, as a potent immunosuppressive agent, butyrate can drive the differentiation of regulatory B cells (Bregs) and enhance their anti-inflammatory functions. B10 cells represent a subset of Bregs that can produce the anti-inflammatory cytokine IL-10. SCFAs (0.5 mM) for 48 h can promote the generation of mouse and human B10 cells

in vitro. Additionally, an increase of B10 cells by 150 mM butyrate has been observed in both healthy mice and mice with DSS-induced colitis. The effects of SCFAs are dependent on HDAC inhibitory activity and are independent of GPCRs. Butyrate, similar to other HDACi, can activate the p38 MAPK signaling pathway to facilitate B10 cell generation (85). Moreover, butyrate at 0.5 mM for 24 h possesses the ability to regulate the differentiation and anti-inflammatory functions of IL-10+IgM+ PCs. Mechanistically, the inhibition of HDAC3 represents a potential pathway through which butyrate induces the differentiation of IL-10+IgM+ PCs and the expression of IL-10 (86). Collectively, these findings demonstrate that SCFAs exhibit regulatory activity on B cell differentiation and function based on HDAC inhibition.

5. System protection of SCFAs via HDAC inhibition

In addition to immune cells, SCFAs also contribute to the regulation of tissue-resident cells, thereby influencing the host's immune equilibrium. Histone acetylation modifications are widely recognized as being associated with key cellular processes under both physiological and pathological conditions. In this section, the relevant findings regarding the host-protective effects (categorized into intestinal and extra-intestinal effects) of microbial SCFAs based on HDAC inhibition are summarized. These highlight that SCFAs regulate the activity and function of intestinal immune cells and IECs through their HDAC inhibitory activity, thereby modulating the local gut immune homeostasis. In particular, SCFAs, mainly acetate, propionate and butyrate, exert intestinal epithelial protective effects by inhibiting class I and class II HDACs (2, 3 and 8) and promoting acetylation modifications of histones H3/H4 and other sites. These protective effects encompass, but are not limited to, the proliferation and apoptosis, anti-bacterial effect, barrier function, absorption and metabolic function, inflammation and immune responses of IECs (Fig. 5). Similarly, the HDAC inhibitory activity and acetylation-modified effects of these SCFAs contribute to tissue protection in extra-intestinal organs such as the liver, kidney, nerves and blood vessels. Mechanistically, SCFAs can inhibit class I and II HDACs (1, 2, 3, 4 and 8) and promote acetylation modifications of histone H3/H4 and other sites. This influences a wide range of activities and functions of various cell types, including hepatocytes and hepatic stellate cells (HSCs) in the liver, renal macrophages and epithelial cells in the kidney, neuronal cells, microglia and astrocytes in the nervous system, and vascular endothelial cells (Fig. 6). The aforementioned findings underscore the systemic protection of SCFAs based on HDAC inhibition, which are associated with the functional regulation of multiple tissue-resident cells both inside and outside the gut.

Inside the gut

Immune cells. SCFAs can alleviate intestinal immune cell inflammation through HDAC inhibition and acetylation modification. For instance, research has revealed that butyrate is more effective than acetate and propionate in markedly reducing LPS-induced expression of pro-inflammatory mediators in both BMDMs and colonic LP macrophages *in vitro* and *in vivo*. This anti-inflammatory effect of butyrate is independent of GPCRs and instead occurs through HDAC inhibition, which increases H3K9 acetylation at the promoter regions of cellular inflammatory genes (39). In addition, under colitis conditions, butyrate can improve anemia and reduce TNF-α production by colonic macrophages. It does so by promoting ferroportin (FPN)-dependent iron export from macrophages, thus regulating iron homeostasis. The FPN-inducing effect of butyrate (1 mM *in vitro*) relies on its inhibitory activity against HDAC at the Slc40a1 promoter (87). Compared with other SCFAs, butyrate (0.0625-0.5 mM) administered for 4 days more effectively reduces the activation, proliferation and production of inflammatory cytokines (such as IFN-γ and IL-17) in human intestinal LP CD4+ T cells *in vitro*. The effects of butyrate can be attributed to its promotion of histone acetylation in both unstimulated and TCR-stimulated CD4+ T cells, as well as through GPR43 signaling (68). Butyrate (used *in vivo* at 200 mM or *in vitro* at 0.5 mM) can also promote IL-22 production by intestinal and circulating CD4+ T cells and ILCs via GPR41 and HDAC inhibition, thereby suppressing intestinal infection and inflammation. Mechanistically, butyrate upregulates the expression of AhR and HIF-1α, which are differentially regulated by mTOR and STAT3, leading to increased IL-22 levels in CD4+ T cells under Th1 conditions. Importantly, butyrate also increases the accessibility of HIF-1α binding sites at the IL-22 promoter in CD4+ T cells through histone modification (69). γδT cells are tissue-resident T cells that carry out innate immune functions and can produce the pro-inflammatory cytokine IL-17, participating in host defense and the regulation of tissue inflammation. A previous study has revealed that the SCFA propionate (200 mM *in vivo* or 1 mM *in vitro*) can directly act on intestinal γδT cell populations and inhibit IL-17 production, with its mechanism of action being associated with HDAC inhibition. Therefore, the impact of propionate on γδT cell activity may provide a potential pathway to prevent chronic intestinal inflammation and cancer progression (88).

IECs. The regulatory roles of microbial SCFAs in the activities and function of IECs through HDAC inhibition are currently under extensive investigation (89-119). These effects of SCFAs are multifaceted, encompassing but not limited to cellular activities such as proliferation, differentiation and anti-bacterial action, as well as cellular functions including absorption, metabolism, inflammation and immunity.

First and foremost, SCFAs can regulate the proliferative activity of IECs via HDAC inhibition or histone acetylation. For instance, 2 mM butyrate can activate the AP-1 response in colonic epithelial cells by inhibiting HDACs. AP-1 is a transcription factor that carries out a key role in determining cell proliferation, differentiation, transformation, cell migration and apoptosis (89). A recent study has demonstrated that butyrate at 150 mM *in vivo* or 1 mM *in vitro* can also restrict the differentiation and proliferation of intestinal tuft cells by inhibiting HDAC3, serving as an important product of the microbiota in calibrating intestinal type 2 immunity (90). Another SCFA, propionate, can promote the spreading and polarization of epithelial cells by inhibiting HDACs and activating GPR43 and STAT3, thereby enhancing the renewal rate and persistence of the intestinal epithelium (91). It is important to emphasize that, by contrast, butyrate exerts an inhibitory effect on the cellular activity of cancerous IECs or can induce

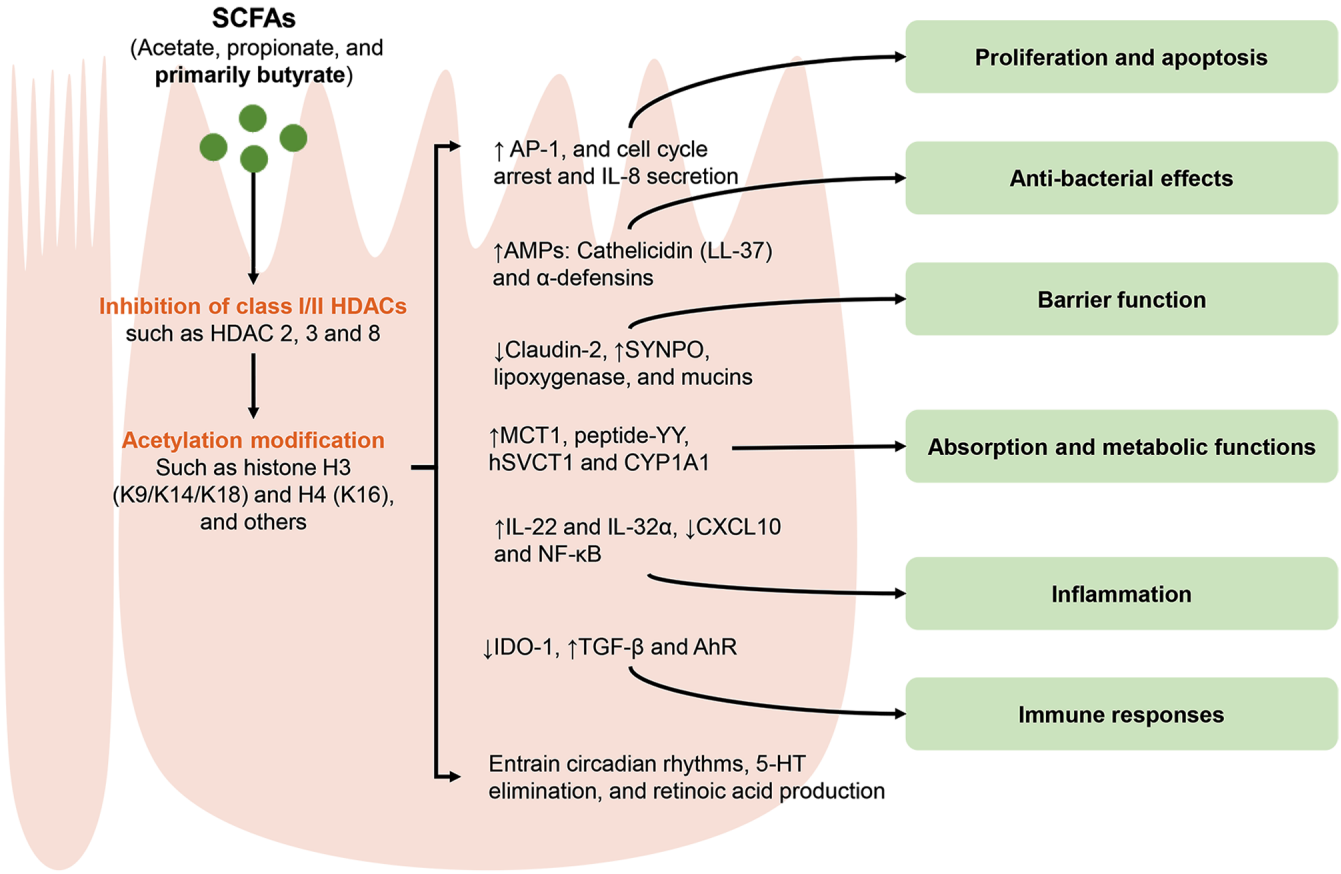

Figure 5. Regulatory effects of SCFAs on the activities and function of IECs through HDAC inhibition. SCFAs, such as acetate, propionate and primarily butyrate, can extensively modulate various cellular signaling pathways by inhibiting class I/II HDACs (2, 3 and 8) and promoting acetylation modifications of histones H3 (K9/K14/K18), H4 (K16) and other sites. Consequently, these actions have a notable impact on the activities and function of IECs. IECs, intestinal epithelial cells; SCFAs, short chain fatty acids; HDACs, histone deacetylases; AP-1, activator protein-1; AMPs, antimicrobial peptides; MCT, monocarboxylate transporters; SYNPO, synaptopodin; hSVCT, human sodium-dependent vitamin C transporters; CYP1A1, cytochrome P450 1A1; CXCL10, C-X-C motif chemokine ligand 10; IDO-1, indolamine 2,3-dioxygenase 1; AhR, aryl hydrocarbon receptor; 5-HT, 5-hydroxytryptamine/serotonin.

apoptosis. For example, Mariadason *et al* (92) revealed that 2 mM butyrate markedly triggers activities such as cell cycle arrest, apoptosis, IL-8 secretion, in undifferentiated colon Caco-2 cells, and consistently, while consistently and selectively inducing high levels of histone hyperacetylation. Previously, it was reported that butyrate could have contradictory effects on the activity of normal colonic epithelial cells and cancer cells. For instance, when exposed to the HDACi butyrate at a concentration of 1-2 mM, colon cancer cell lines exhibit a notable increase in alkaline phosphatase activities, urokinase receptor expression and IL-8 secretion. By contrast, butyrate inhibits alkaline phosphatase activities in the primary normal cells but markedly suppresses urokinase receptor and IL-8 secretion (93). Another example is that 5 mM butyrate can inhibit cell proliferation and stimulate cell differentiation in the colon cancer cell line HT-29. The effects of butyrate in this cell line stem from the induction of cyclin D3 and p21, as well as its role as an HDACi in promoting histone H4 hyperacetylation (94).

AMPs are potent defensive molecules released by IECs that participate in innate immunity, carrying out a key role in maintaining mucosal homeostasis (95). Current research has yielded substantial evidence indicating that HDACs affect the expression of relevant defense genes. In particular, the regulatory function of microbial SCFAs as HDACi in modulating the anti-bacterial activity of IECs, mediated by AMPs, is being gradually elucidated. For example, Fischer *et al* (95) has indicated that inhibiting HDAC activity can enhance AMP production from IECs upon bacterial challenge, without increasing the expression of inflammatory cytokines. Cathelicidin (LL-37) is a major AMP within the intestinal non-specific innate immune system. The SCFA butyrate (2-4 mM) can induce the expression of LL-37 in a time-dependent manner in gastrointestinal cancer cells that lack LL-37. The induction of LL-37 by butyrate is due to the parallel acetylation of histone H4 and non-histone HMGN2, and is associated with the suppression of MEK-ERK signaling pathway (96). α-defensins, also known as cryptdins, are the primary bactericidal AMP molecules produced by intestinal Paneth cells and their activation requires MMP7. SCFAs, including butyrate, propionate and acetate, induce the expression of α-defensins and MMP7 in Paneth cells *in vitro*. Histone deacetylation (specifically HDAC8 inhibition) and STAT3 might be involved in the butyrate (1-2 mM)-mediated induction of α-defensin, contributing to the restoration of the intestinal anti-microbial barrier function (97). However, not all regulation of AMP genes by SCFAs is determined by inhibiting HDAC activity. For instance, the induction of host

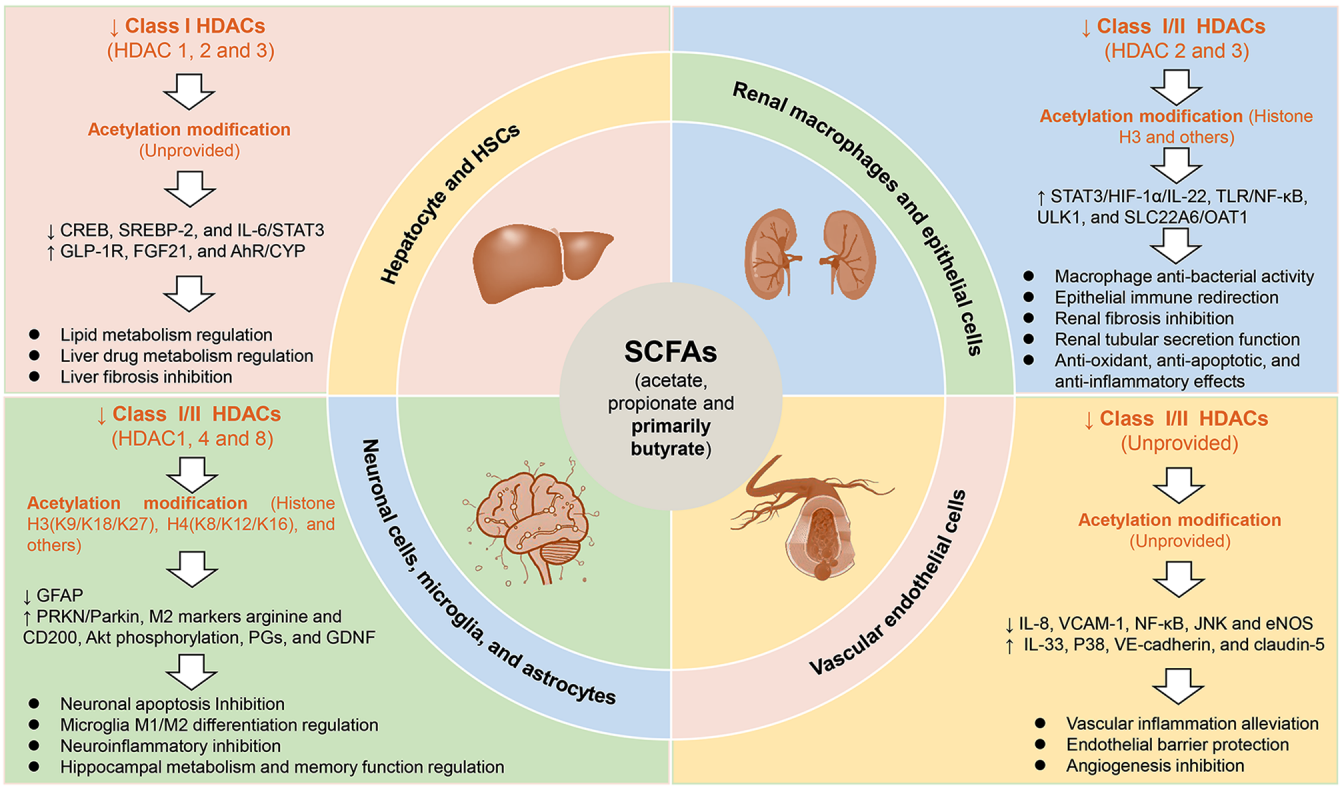

Figure 6. The extraintestinal protective effects of SCFAs based on HDAC inhibition. The SCFAs, namely acetate, propionate and primarily butyrate, exert immunoprotective effects on extra-intestinal organs, including the liver, kidney, nerves and blood vessels. These effects are achieved through the mechanism of HDAC inhibition. Mechanistically, SCFAs are capable of inhibiting the activities of class I and II HDACs (1, 2, 3, 4 and 8), while simultaneously regulating acetylation modifications at histone H3 (K9/K18/K27), H4 (K8/K12/K16) and other sites. These actions modulate the activities and functions of different tissue-resident cells, ultimately contributing to the systemic protection of SCFAs. SCFAs, short chain fatty acids; HDAC, histone deacetylase; CREB, cyclic adenosine monophosphate response element binding protein; SREBP, sterol regulatory element-binding transcription factor; GLP-1R, glucagon-like peptide-1 receptor; FGF21, fibroblast growth factor 21; AhR, aryl hydrocarbon receptor; CYP, cytochromes P450; GFAP, glial fibrillary acidic protein; PRKN, parkin RBR E3 ubiquitin protein ligase; M1, macrophage subset 1; M2, macrophage subset 2; PGs, prostaglandins; GDNF, glial cell line derived neurotrophic factor; HSCs, hepatic stellate cellsHIF-1α, hypoxia inducible factor-1α; TLR, toll-like receptor; ULK1, unc-51 like autophagy activating kinase 1; SLC22A6, solute carrier family 22 member 6; OAT1, organic anion transporter-1; VCAM-1, vascular cell adhesion molecule-1; eNOS, endothelial nitric oxide synthase.

defense peptides, namely pBD3 and pEP2C, by butyrate in porcine IECs (IPEC J2) is associated with the expression of TLR2 and EGFR, rather than HDAC inhibition (98).

HDAC inhibition carries out a key role in how SCFAs maintain the barrier function of IECs. Representative SCFAs, namely butyrate, propionate and acetate, reduce the activation of epithelial Caco-2 cells induced by inflammatory cytokines such as TNF-α, IFN-γ and IL-1β. In particular, butyrate (0-8 mM) exerts a pronounced dose-dependent preventive effect on inflammation and inflammation-induced barrier disruption in both inflammation-induced Caco-2 cells and co-culture models of PBMCs/Caco-2 cells. Additionally, butyrate can regulate the release of inflammatory cytokines from activated PBMCs and immune cell phenotypes. Meanwhile, the HDACi can replicate the epithelial barrier-protective effect of butyrate (99). Notably, the mechanisms by which SCFAs, mainly butyrate, enhance IEC barrier function by inhibiting HDAC expression are currently being elucidated (100-103). For example, one study showed that butyrate (5 or 10 mM) can suppress the expression of claudin-2, a permeability-promoting tight-junction protein, in IECs in an IL-10RA-dependent manner. This suppression is achieved through the combined actions of HDAC inhibition (H3K9 acetylation) and STAT3 activation (100). The actin-binding protein synaptopodin (SYNPO) is localized within intestinal epithelial tight junctions (TJs) and F-actin stress fibers, carrying out a key role in maintaining barrier integrity and cell motility. The mechanism underlying the relationship between butyrate (5 mM) and epithelial barrier restoration likely involves the induction of SYNPO expression through HDAC inhibition in both epithelial cell lines and murine colonic enteroids (101). Furthermore, 1 mM butyrate can reduce TJ permeability in intestinal monolayers by activating lipoxygenase and the HDACi TSA mimics this effect of butyrate (102). When butyrate (2 mM for 24 h) serves as an energy source for the human polarized colonic goblet cell line HT29-Cl.16E, it promotes the expression of mucin (MUC) genes that protect the epithelial barrier. It is noteworthy that the HDAC inhibitory action of butyrate can participate in regulating the expression of MUC3 gene, yet it does not affect the expression of the MUC2, MUC5AC and MUC5B genes (103).

SCFAs can regulate the absorption and metabolic function of IECs through HDAC inhibition. Indeed, the representative SCFA, butyrate, serves as the primary energy source for colonic cells. However, the absorption of butyrate is not actually secondary to its inhibition of HDACs. A study has demonstrated that butyrate at 5 mM for 24 h activates the MCT1 promoter via the NF-κB pathway rather than through

HDAC, leading to an enhanced absorption of SCFAs in Caco-2 cells (104). Consequently, as the effective HDACi, SCFAs carry out a more notable role in regulating the absorption and metabolic behaviors of nutrients or other exogenous substances in the IECs. For instance, when propionate and butyrate are each administered at 2 mM for 24 h, they considerably increase the expression of peptide-YY (PYY) in both human intestinal cell lines and mouse primary cells. PYY is an important hormone secreted by heterogeneous enteroendocrine cells that is involved in food intake and insulin secretion. This effect is primarily attributed to the HDAC-inhibitory activity of SCFAs and the partial role of FFA2, also known as GPR43 (105). Butyrate can also mediate epigenetic regulation of the sodium-dependent vitamin C transporters (such as hSVCT1) by inhibiting HDAC isoforms 2 and 3, thereby regulating the absorption of vitamin C in the intestinal epithelium (106). Nevertheless, butyrate also has the ability to regulate the metabolism of cytotoxic substances in epithelial cells. Sodium butyrate (0.5 mM) can induce the acetylation of histone H3 (at Lys14) and histone H4 (at Lys16) in colonic epithelial cells. This action triggers the expression of cytochrome P450 1A1 (CYP1A1), a metabolic enzyme for dietary carcinogens such as benzo[a]pyrene (BaP) (107).

The regulatory role of SCFAs in epithelial inflammation can also be partially attributed to the inhibition of HDAC. Specifically, SCFAs can directly modulate the cytokine releasing of IECs through inhibiting HDAC activity. For instance, butyrate at 3 mM for 16 h can markedly enhance the signaling of the protective cytokine IL-22 in human epithelial Caco-2 and DLD1 cells. Independently of IL-22R1 regulation, butyrate can increase the accessibility of STAT3 at affected gene loci, and this mechanism is associated with HDAC inhibition (108). When administered at the same concentration of 10 mM for 12 h, butyrate, rather than acetate and propionate, can stimulate the expression of the cytotoxic pro-inflammatory cytokine IL-32α in IEC lines, namely HT-29, SW480 and T84. Additionally, butyrate can enhance IL-1β-induced expression of IL-32α mRNA. This effect is not associated with the activity of PI3K, a mechanism involved in IL-32α expression. Instead, it predominantly depends more heavily on the inhibition of HDACs (109). When compared with acetate and propionate, 2 mM butyrate emerges as the most potent inhibitor in preventing the release of CXCL10 from the IEC HT-29 cells activated by IFN-γ and IFN-γ+TNF-α. This action contributes to reducing epithelial inflammation, maintaining immune homeostasis and upholding the integrity of the gut barrier. Butyrate also inhibits the protein expression of IRF9 and phosphorylated JAK2, along with the mRNA expression of CXCL10, SOCS1, JAK2 and IRF9 in cells. By inhibiting HDAC activity, butyrate prevents the epithelial release of CXCL10, with an effect comparable with that of the well-known HDACi such as TSA (110). The impact of butyrate on the colonic inflammatory response is partly due to its regulation on NF-κB activation based on HDAC inhibition. Exposure of HT-29 cells to 4 mM butyrate for 18 h eliminates their constitutive NF-κB p50 dimer activity. Another notable finding is that butyrate selectively regulates NF-κB activation. It can markedly suppress the activation of NF-κB triggered by TNF-α and phorbol ester, while enhancing the NF-κB activation induced by IL-1β. The regulatory effect of butyrate on NF-κB may be partially attributed to its ability to inhibit HDACs, as the HDACi TSA exerts a similar effect (111).

SCFAs, primarily butyrate, also possess regulatory effects on the immune activity of IECs, which can be influenced by the HDAC inhibitory activity. For instance, butyrate (0.5-8 mM; 24 h) can modulate the expression of the immune effector indolamine 2,3-dioxygenase 1 (IDO-1) in both human primary IECs and IEC cell lines. Independent of the transcriptional mechanisms involving GPCRs (GPR41, GPR43 and GPR109a), butyrate downregulates IDO-1 expression through a dual mechanism: A reduction in STAT1 levels and its HDAC inhibitory property (112). The SCFA butyrate also regulates host T-cell responses by interacting with IECs to improve the intestinal mucosal immune system. One notable effect is the enhancement of the accumulation of anti-inflammatory Treg cells in the gut. *In vitro* studies have demonstrated that butyrate can induce the TGF-β production in primary IEC cells or cell lines, promoting the expression of Foxp3 and the anti-inflammatory cytokine IL-10 under Treg conditions. This inductive effect of butyrate is independent of GPCRs and their associated signaling pathways but relies on HDAC inhibition mediated by SP1 (113,114). A study has shown that SCFAs (acetate, propionate and butyrate) and AhR play similar protective roles in intestinal inflammation and Treg cell induction. In particular, 5 mM butyrate markedly increases the expression of AhR-responsive genes (such as Cyp1a1/CYP1A1) in mouse colon cells YAMC and human colon cells Caco-2. The HDACi, including panobinostat and vorinostat, exhibit effects similar to those of SCFAs. They enhance AhR ligand-mediated induction and subsequent histone acetylation (115). Modoux *et al* (116) have uncovered that butyrate is not an AhR ligand but acts as an HDACi to remodel chromatin. By synergizing with known ligands, butyrate increases the recruitment of AhR to the promoters of target genes, thereby enhancing AhR activation.

Moreover, when SCFAs act as HDACi, they can also influence intestinal epithelial homeostasis through alternative pathways (117-119). For instance, previous research has disclosed that SCFAs (primarily 1 mM butyrate) produced by gut microbiota can entrain intestinal epithelial circadian rhythms via an HDACi-dependent mechanism. This finding deepens the comprehension of how the microbial and circadian rhythm networks jointly regulate intestinal epithelial homeostasis (117). Both treatment with the HDACi butyrate (5 mM) and TSA (1 μM) for 24 h can reduce the expression of the serotonin (5-HT) transporter (SERT) in Caco-2 cells. Consequently, this reduction promotes the clearance of extracellular 5-HT. Reduced SERT expression and the subsequent high levels of 5-HT are associated with various intestinal diseases, such as inflammation or intestinal infections. The mechanism by which butyrate and TSA downregulate intestinal SERT involves the inhibition of HDAC2 and an increased binding of acetylated histone H3 or H4 to the human SERT (hSERT) promoter 1 (hSERTp1) (118). Moreover, the SCFA butyrate at 2 mM for 24 h has the ability to stimulate the production of retinoic acid in the IEC cell line through HDAC3 inhibition (resulting in H3K18 acetylation), thereby promoting mucosal homeostasis. This is attributed to the fact that IECs play a key role in upholding mucosal immune homeostasis, through the production of retinoic acid (119).

Outside the gut

Hepatic protection. Current evidence indicates that among SCFAs, butyrate primarily exerts regulatory effects on the activity and function of hepatocytes through HDAC inhibition. The HDACi action of butyrate is mainly associated with the metabolic functions of the liver, with a particular emphasis on lipid metabolism. For instance, Zheng *et al* (120) discovered that butyrate (at 2 mM *in vitro* and 5% butyrate by weight *in vivo*) can suppress lipogenic genes and activate genes related to lipid oxidation in hepatocytes. As a result, it ameliorates hepatic steatosis and abnormal lipid metabolism in mice fed with high-fat and fiber-deficient diets. The underlying molecular mechanism of butyrate has been elucidated as the activation of the liver GPR41/43-mediated CaMKII-CREB signaling pathway and the inhibition of the HDAC1-CREB signaling pathway. Glucagon-like peptide-1 (GLP-1) is a protein involved in regulating metabolic processes and has a beneficial effect on non-alcoholic fatty liver disease and steatohepatitis. The study has shown that butyrate can reverse the decline in hepatic GLP-1 caused by a high-fat diet and alleviate hepatic steatosis. From a mechanistic perspective, butyrate (5 mM) for 24 h enhances the expression of GLP-1R in liver HepG2 cells by inhibiting HDAC2, rather than through the activity of GPR43/GPR109a (121). In addition, butyrate (500 mg/kg body weight and 0.5 mM, respectively) can induce the gene expression of FGF21 in the liver and HepG2 cells by inhibiting HDAC3. FGF21 is known to stimulate fatty acid oxidation and ketone body production (122). Similar to the HDACi TSA, 5 mM butyrate can also effectively reduce the cholesterol content in HepG2 cells, suggesting that HDAC inhibition is its underlying mechanism of action. Importantly, the potential mechanisms by which these HDACi regulate hepatic cholesterol metabolism are also associated with impaired SREBP-2 signaling (123). Butyrate also exerts regulatory effects on hepatic drug metabolism. Cytochromes P450 (CYPs) are key enzymes in liver drug metabolism. A previous study has shown that butyrate (1-5 mM) can activate the AhR receptor and increase the expression of its target gene CYP in the liver cell line HepG2-C3 and primary human hepatocytes. The activation of hepatic AhR by butyrate may be attributed to the epigenetic regulatory effect of HDAC inhibition (124). The activation of HSCs is closely associated with the development of liver fibrosis. Notably, HDACs are key regulators of HSC activation. Zhao *et al* (125) revealed that the HDACi butyrate can inhibit the activity of liver stellate cells LX2 by inhibiting HDAC2 and the subsequent activation of the IL-6/STAT3 pathway. The *in vivo* study has also demonstrated that butyrate (0.3 mg/g) can alleviate liver fibrosis in bile duct ligation mice and improve the intestinal microenvironment by inhibiting the HDAC2/IL-6/STAT3 pathway.

Renal protection. SCFAs are also recognized as a key class of renal protectants. Leveraging their HDAC inhibitory activity, SCFAs can markedly contribute to the bactericidal activity of head kidney macrophages (HKMs). Research conducted by Zhang *et al* (126) has shown that the SCFA butyrate (10 mM; 24 h) can activate the STAT3/HIF-1α/IL-22 signaling pathway through HDAC3 inhibition and GPCR action, thereby inducing HKM autophagy that aids in pathogen clearance. Further evidence suggests that SCFAs exert renoprotective effects by modulating the activity and function of renal epithelial cells through HDAC inhibition. As effective HDACi, treatment with butyrate (10 mM), propionate (10 mM) and TSA (2 μM) each for 30 min can all result in a rapid increase in histone acetylation in renal-derived epithelial cells 293 and enhance NF-κB activation induced by TLR agonists. This indicates that SCFAs can rapidly alter the epigenetic state of epithelial cells, resulting in the redirection of epithelial immune responses (10). SCFAs propionate and butyrate administered orally at 300 mg/kg/day for 8 weeks can trigger autophagy in renal tubular cells and alleviate renal fibrosis in diabetic mice. They achieve this by inhibiting HDAC2, which promotes histone H3 acetylation in the ULK1 promoter and facilitates the transcription of downstream genes (127). When applied at a concentration of 1 mM each for 24 h, butyrate and propionate can notably increase the activity of the organic anion transporter-1 by upregulating the SLC22A6 gene, thereby regulating the secretory function of renal tubular cells and maintaining kidney health. It has been shown that SCFAs operate independently of GPCR activation and instead exert their effects by inhibiting the expression of class II HDAC genes (128). Importantly, the renoprotective effects of butyrate, a representative HDACi, on epithelial cells extend far beyond these mechanisms. For instance, butyrate (1 mM) can act as an anti-oxidant and inhibit apoptosis in high glucose-induced normal rat kidney tubular epithelial (NRK-52E) cells, with its mechanism of action related to HDAC2 inhibition (129). Moreover, butyrate (400 mg/kg, i.p.) can ameliorate proteinuria and alleviate glomerulosclerosis and tissue inflammation by maintaining podocytes in the glomerular basement membrane through epigenetic and GPR109a-mediated mechanisms. The protective effects of butyrate are associated with an increase in podocyte-related proteins and the restoration of acetylation and methylation at their gene promoter sites (130).

Neuroprotection. SCFAs are considered highly promising neuroprotective and anti-inflammatory agents, playing a key role in the activity and function of neuronal cells as well as glial cells, including as microglia and astrocytes. Importantly, SCFAs may act as neuroprotective agents due to their HDAC inhibitory properties (131-140).

Primarily, butyrate, which serves as a major component of SCFAs, exerts direct protective effects on neuronal cells through HDAC inhibition and subsequent histone acetylation. Research has revealed that metabolic disturbances in SCFAs, mainly characterized by low levels of butyrate, are associated with an increase in neuronal apoptosis. This phenomenon occurs as a result of the elevated expression of HDAC4 in the rat hippocampus and the consequent alteration of H4K8ac, H4K12ac and H4K16ac. This finding underscores the notable neuroprotective potential of butyrate, as it can inhibit the HDAC4-mediated neuronal apoptosis pathway via the gut-brain axis (131). Excessive mitochondrial accumulation in diabetes represents one of the leading causes of cognitive impairment, as it induces neuronal apoptosis. A study conducted by Cho *et al* (132) revealed that butyrate (500 μM; 30 min) can ameliorate high glucose-induced neuronal mitophagy dysfunction and neuronal apoptosis by restoring PRKN/Parkin expression levels. This positions butyrate as an important active component in protecting against diabetes-related cognitive impairment. Mechanistically, butyrate primarily restores the PRKN-mediated neuronal mitophagy function by inhibiting the RELA-HDAC8 complex.

Microglia represent a distinct type of glial cells within the nervous system, endowed with phagocytic capabilities. Their abnormal activation is associated with inflammation in the central nervous system. Microglia manifest two distinct phenotypes: The M1 phenotype predominantly produces pro-inflammatory mediators, whereas the M2 phenotype releases anti-inflammatory factors that are involved in immunosuppression and neuroprotection. SCFAs can directly modulate the activity and function of microglia, which are the innate immune cells in the brain, thereby alleviating neuroinflammation. For instance, propionate and butyrate given orally at 300 mg/kg each for 7 days can reduce the activation of microglia and the levels of pro-inflammatory cytokines, as well as inhibit HDAC1 expression levels and promote the H3K9 acetylation in the brains of GF rats (133). Notably, butyrate emerges as a key SCFA in regulating microglial activity. A study has shown that butyrate (0.1 mM; 1 and 10 mM) can polarize the M1 phenotype of microglia towards the M2 phenotype after oxygen and glucose deprivation. Acting as an HDACi, butyrate suppresses the expression of pro-inflammatory genes CD86 and IL1-β in microglia, and increases the expression of anti-inflammatory M2 markers, arginase and CD200 (134). Butyrate at a concentration of 1.2 mM, along with other HDACi, can markedly induce apoptosis and attenuate the pro-inflammatory response in microglia activated by LPS. This process is accompanied by a loss of mitochondrial membrane potential and hyperacetylation of histone H3 (135). The study by Wang *et al* (136) confirmed the anti-inflammatory effect of butyrate in LPS-induced microglia from the perspective of microglial process elongation. They discovered that 5 mM butyrate could promote Akt phosphorylation and subsequent functional elongation of microglial processes, thereby alleviating neuroinflammation, an effect associated with HDAC inhibition (136). However, low concentrations of butyrate (0.01-1 mM) can markedly enhance the inflammatory response of LPS-induced microglia. The effects of butyrate include promoting the release of prostaglandins (PGs) such as PGE2, PGD2 and 8-iso-PGF2α, as well as the release and gene expression of pro-inflammatory cytokines, without affecting the activation of MAPKs p38, ERK1/2 and JNK signaling pathways. Importantly, the promoting effect of butyrate on PGs release from activated microglia is associated with histone acetylation at the H3-K18 site (137).

SCFAs, primarily butyrate, exhibit neuroprotective activity in astrocytes by exerting HDAC inhibitory effects. Research by Wu *et al* (138) revealed that the astrocyte-protective role of butyrate, mediated by HDAC inhibition, could serve as a potential therapeutic target for neurodegenerative diseases such as Parkinson's disease. This is attributed to the fact that butyrate (1.2 mM), similar to other HDACi such as VPA and TSA, protects dopaminergic neurons in neuron-glia cultures and upregulates the expression of astrocyte-derived neurotrophic factors, glial cell line derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor. The effects of butyrate rely, at least partially, on HDAC inhibition, which increases GDNF promoter activity and induces hyperacetylation of histone H3 associated with the GDNF promoter. Furthermore, the HDAC inhibitory effect of butyrate is pivotal for preserving energy metabolism and memory function in hippocampal astrocytes. However, a maternal high-fructose diet can disrupt butyrate signaling and subsequent HDAC4-mediated epigenetic changes, leading to reduced mitochondrial function in the hippocampus (139). Nevertheless, the HDAC inhibitory effect of butyrate can occasionally restrict astrocyte activity to sustain normal neural function. For instance, butyrate (5 mM; 24 h) diminishes the expression of glial fibrillary acidic protein (GFAP), the main intermediate filament in astrocytes, in both primary human astrocytes and astrocytoma cells through HDAC inhibition (H3K27 acetylation). Conversely, dysregulation of gene expression of histone acetylation can lead to GFAP aggregation, which is a hallmark of human diseases such as Alexander's disease (140).

Vascular protection. SCFAs primarily exhibit vascular protective activity by ameliorating endothelial inflammation through the inhibition of HDACs. For instance, research conducted by Li *et al* (141) revealed that SCFAs are capable of suppressing the endothelial inflammatory responses induced by LPS or TNF-α, as well as the overexpression of vascular cell adhesion molecule-1. The underlying mechanisms are associated with the activation of GPR41/43 or the inhibition of HDACs in human umbilical vein endothelial cells (HUVECs). Specifically, the activation of GPR41/43 mediates the effects of acetate on IL-6 and IL-8 production, along with the effects of propionate and butyrate on IL-6 production. Additionally, HDAC inhibition mediates the impacts of propionate (0.3 mM) and butyrate (0.1 mM) for 12 h on IL-8 production, VCAM-1 expression, and the adhesion of PBMC to an endothelial monolayer. Furthermore, the researchers also validated the anti-inflammatory mechanisms of propionate and butyrate in TNF-α-induced endothelial activation. It was discovered that the HDACs/IL-33/NF-κB pathway mediates their inhibitory activity on endothelial IL-8 production. By contrast, the HDACs/MAPK signaling pathway, rather than IL-33, is involved in their inhibitory effect on VCAM-1 expression (142). These findings contribute to the understanding of the endothelial-protective effects of SCFAs based on HDAC inhibition.

Besides the aforementioned effects, SCFAs confer other forms of vascular protection through HDAC inhibition, including endothelial barrier protection and angiogenesis inhibition. For example, acetate, propionate and butyrate have all been found to effectively reduce paracellular permeability, thereby protecting the endothelial barrier. Propionate and butyrate at low concentrations of 1 and 0.5 mM, respectively, can decrease paracellular permeability in HUVECs without inducing cell damage, whereas acetate reduces paracellular permeability in a concentration-dependent manner. Notably, the HDACi TSA at lower concentrations also reduce paracellular permeability, suggesting the potential for HDAC inhibition in mediating SCFA-induced endothelial barrier protection (143). Butyrate, in particular, carries out a pivotal role in maintaining endothelial integrity and renal metabolic homeostasis. It can reduce the proliferation of human glomerular microvascular endothelial cells (hgMVECs), strengthen the endothelial barrier by increasing the expression of VE-cadherin and claudin-5, and promote mitochondrial biogenesis. Additionally, butyrate mitigates the LPS-induced increase in oxygen consumption to protect mitochondrial function in hgMVECs (144). Endothelial NOS (eNOS)-derived NO carries out a role in the vasorelaxation and angiogenesis

signaling of endothelial cells. Class I and II HDACi can effectively suppress angiogenesis stimulated by hypoxia or vascular endothelial growth factor. Butyrate (10 μM), along with other HDACi such as TSA (1 μM) and MS-275 (10 μM), can reduce the expression of both eNOS protein and mRNA in HUVECs (145).

6. The potential therapeutic effects of SCFAs as HDACi in diseases

At present, epigenetics has emerged as a promising field for elucidating the pathogenesis of human diseases. Epigenetic regulation does not alter the genomic sequence but can affect gene expression, cellular function and susceptibility to diseases. Importantly, epigenetic modifications are intricate and reversible, depending on multiple variable factors. Consequently, epigenetic therapies hold great promise as innovative treatment modalities for human diseases (146,147). Acetylation modification by HDAC is a common form of epigenetic regulation. HDACs are responsible for the deacetylation of histones and non-histone proteins, serving as key regulators of gene transcription and cellular functions. Over the years, HDACs have been recognized as key therapeutic targets for a wide range of human diseases, including tissue fibrosis, autoimmune/inflammatory diseases, metabolic disorders and neurological diseases (148). Currently, HDACi that block the activity of specific or a range of HDACs have become potential epigenetic regulators, carrying out a key role in the treatment of human diseases. Notably, several HDACi approved by the US Food and Drug Administration, including belinostat, panobinostat, romidepsin, suberoylanilide hydroxamic acid (SAHA) and VPA. These inhibitors exhibit remarkable anti-inflammatory properties that contribute to the improvement of various inflammatory diseases (149). Furthermore, certain HDACi, such as VPA, SAHA and TSA, also possess neuroprotective effects and have demonstrated considerable therapeutic efficacy in neurological diseases (150). The aforementioned findings suggest that these HDACi may possess therapeutic potential in maintaining host immune homeostasis across various diseases through epigenetic regulation.

It is widely acknowledged that SCFAs are vital microbial metabolites that represent a class of potential HDACi to markedly impact human health. As previously discussed, acetate, propionate and butyrate, which are key components of SCFAs, can act as HDACi to exert immunomodulatory effects at both the immune cells and systemic levels. In particular, the HDAC-inhibitory activity of SCFAs can induce immunomodulatory and tissue-protective effects not only within the local intestinal milieu but also in extra-intestinal organs, such as the liver, kidneys, nerves and blood vessels. The aforementioned findings suggest that SCFAs hold great promise as effective HDACi for maintaining host immune homeostasis. To date, the therapeutic potential of SCFAs through HDAC inhibition in various immune-related diseases, including both intestinal and extraintestinal conditions, is being extensively investigated. Therefore, this section aims to provide a concise summary of the relevant findings, which are systematically compiled in the Table I (80,81,151-155), Table II (120,121,125,156-158), Table III (127,129,159-161), Table IV (132,162-165), Table V (166-168), and Table VI (35,169-175).

Table I. Potential therapeutic effects of SCFAs as HDACis in intestinal diseases.

Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Butyrate	DSS-induced colitis	Enhance intestinal epithelial barrier function and ameliorate intestinal inflammation	IECs	Histone acetylation	Inhibit the HDAC8/NF-κB pathway to enhance Slc26a3 expression	(151)
	DSS-induced colitis	Ameliorate intestinal inflammation	IECs and Macrophages	Histone H3 acetylation	Unprovided	(152)
	DSS-induced colitis	Ameliorate intestinal inflammation	Neutrophils	Histone H3 acetylation	Inhibit HDAC9	(153)
	DSS- and TNBS-induced colitis	Maintain Th17/Treg balance and ameliorate intestinal inflammation	T cells (Th17/Treg cells)	Acetylation-promoted degradation of c-Myc	Inhibit HDAC1 and 3	(80,81)
Propionate	DSS-induced colitis	Modulate the function of macrophages and ameliorate intestinal inflammation	Macrophages	Histone acetylation	Inhibit HDAC1 and 2	(154,155)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; DSS, dextran sodium sulfate; TNBS, 2,4,6-trinitro-benzenesulfonicacid; IECs, intestinal epithelial cellsSLC26A3, solute carrier family 26 member 3.

Table II. Potential therapeutic effects of SCFAs as HDACi in liver diseases.

Authors, year	Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Zhang *et al*, 2024	Butyrate	Alcoholic liver disease (ALD)	Regulate macrophage polarization and suppresses hepatic inflammation	Macrophages	Unprovided	Inhibit HDAC1/miR-155 axis	(156)
Zhao *et al*, 2025		Biliary atresia-induced liver fibrosis	Alleviate liver fibrosis	HSCs	Unprovided	Inhibit HDAC2/IL-6/STAT3 pathway	(125)
Zhou *et al*, 2018		High-fat diet-induced non-alcoholic steatohepatitis	Alleviate hepatic steatosis	Hepatocytes	Unprovided	Inhibit HDAC2 to increase hepatic GLP-1R expression	(121)
Zheng *et al*, 2023		High-fat and fiber-deficient diet-induced Non-alcoholic fatty liver disease	Attenuate hepatic steatosis and improve hepatic lipid metabolism	Hepatocytes	Unprovided	Regulate GPR41/43-CaMKII/ HDAC1-CREB pathway	(120)
Sun *et al*, 2014		Ischemia reperfusion-induced liver injury	Attenuate hepatic injury and inflammation	Unprovided	Histone H3 acetylation	Unprovided	(157)
Olaniyi and Amusa, 2020	Acetate	Streptozotocin-nicotinamide-induced diabetes mellitus	Alleviate hepatic lipid dysregulation and its accompanied injury	Unprovided	Unprovided	Inhibit HDACs	(158)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; ALD, alcoholic liver disease; HSCs, hepatic stellate cells; GLP-1R, glucagon-like peptide-1 receptor; GPR41/43, G protein-coupled receptor 41/43; CaMKII, calcium/calmodulin-dependent protein kinase II; CREB, cyclic adenosine monophosphate response element binding protein.

Table III. Potential therapeutic effects of SCFAs as HDACi in kidney diseases.

Authors, year	Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Liu *et al*, 2021	Acetate, propionateor butyrate	Folic acid-induced acute kidney injury and subsequent chronic kidney injury	Attenuate both acute and chronic kidney inflammation and reduce fibrosis	Unprovided	Unprovided	Inhibit HDAC3, 4, 5 (butyrate), 7 and 10	(159)
Ma and Wang, 2022	Propionate or butyrate	STZ-induced diabetes mellitus	Enhance autophagy of renal tubular cells and attenuate renal fibrosis	Renal tubule cells	Histone H3 acetylation	Inhibit HDAC2 to increase ULK1 expression	(127)
Du *et al*, 2020	Butyrate	Diabetes mellitus (db/db)	Relieve renal damage and renal tubular cell apoptosis	Renal tubular cells	Unprovided	Inhibit HDAC2	(129)
Khan and Jena, 2014		STZ-induced diabetes mellitus	Ameliorate the fibrogenesis, apoptosis and DNA damage in the kidney	Unprovided	Unprovided	Inhibit HDAC	(160)
Al-Harbi *et al*, 2018	Acetate	Sepsis-induced AKI	Attenuate oxidative stress in T cells	T cells	Unprovided	Inhibit HDAC to suppress NOX2/ROS signaling	(161)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; STZ, streptozotocin; AKI, acute kidney injury; DNA, deoxyribonucleic acid; ULK1, unc-51 like autophagy activating kinase 1; NOX2, NADPH oxidase 2; ROS, reactive oxygen species.

Table IV. Potential therapeutic effects of SCFAs as HDACi in nervous diseases.

Authors, year	Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Li *et al*, 2022	Propionate and/or butyrate	Chronic postsurgical pain-related cognition dysfunction	Alleviate pain-induced cognitive deficits	Unprovided	H4K12 and lysine acetylation	Inhibit HDAC and increase ACCS2	(162)
Patnala *et al*, 2017	Butyrate	Ischemic stroke	Mitigate microglia-mediated neuroinflammation	Microglia	H3K9 acetylation	Inhibit HDAC	(163)
Sharma *et al*, 2015		6-OHDA-induced Parkinson's disease	Improve behavioral abnormalities and attenuate oxidative stress and neuroinflammation	Unprovided	Histone H3 acetylation	Unprovided	(164)
Cho *et al*, 2024		STZ-induced diabetes mellitus	Ameliorate neuronal mitophagy	Neurons	Histone H3 acetylation	Inhibit RELA-HDAC8 complexes to restore PRKN expression	(132)
Soliman *et al*, 2012	Acetate	LPS-induced neuroinflammation	Attenuate neuroglial activation and neuroinflammation	Neuroglia	Histone H3K9, H4K8 and H4K16 acetylation	Inhibit HDAC7	(165)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; 6-OHDA, 6-hydroxydopamine; STZ, streptozotocin; LPS, lipopolysaccharide; ACSS2, acetyl-CoA synthetase2; RELA, RELA proto-oncogene, PRKN, parkin RBR E3 ubiquitin protein ligase.

Table V. Potential therapeutic effects of SCFAs as HDACi in vascular diseases.

Authors, year	Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Moleón *et al*, 2023	Acetate or butyrate	TLR7-induced systemic lupus erythematosus	Prevent vascular dysfunction and elevated blood pressure and mitigate vascular oxidative stress	Unprovided	Unprovided	Inhibit HDAC3	(166)
Ma *et al*, 2023	Butyrate	High-fat diet (HFD)-induced atherosclerosis	Regulate macrophages polarization and ameliorate atherosclerotic inflammation	Macrophages	Unprovided	Inhibit HDAC3	(167)
Karoor *et al*, 2021		Hypoxia-induced pulmonary hypertension	Attenuate pulmonary vascular remodeling and inflammation	Microvascular endothelial cells	Histone H3 acetylation	Unprovided	(168)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; TLR7, toll-like receptor 7; HFD, high-fat diet.

A review of these findings reveals that acetate, propionate and butyrate display a wide spectrum of therapeutic activities against diseases associated with, but not limited to, the intestine, liver, kidney, nerves and blood vessels (Fig. 7). These SCFAs are capable of effectively inhibiting class I and II HDACs while promoting histone acetylation. Consequently, they facilitate disease remission by influencing downstream genes such as NF-κB, miR-155 and GLP-1R. This thus leads to the favorable outcomes such as inflammation resolution, reduced tissue damage and metabolic regulation. Importantly, the regulatory effects of SCFAs, especially butyrate, as HDACi can be directly observed in certain immune and non-immune cells. For example, butyrate can act on IECs, macrophages, neutrophils and T cells to inhibit HDACs and promote histone acetylation, thereby regulating gene transcription and alleviating colonic inflammation. Additionally, butyrate suppresses the activity of HDAC1/2 in hepatocytes, HSCs and macrophages, thereby resulting in its anti-inflammatory, anti-fibrotic and lipid metabolism regulatory effects in the liver. These findings indicate that SCFAs, when functioning as HDACi, are equipped with intricate regulatory mechanisms. They directly inhibit HDAC activity and promote histone acetylation to regulate the transcriptional activity of downstream genes, ultimately modulating the activity and function of immune and non-immune cells. These findings further elucidate that the considerable HDAC-inhibitory activity of SCFAs thus generated promotes their potential as therapeutic agents, contributing to the maintenance of immune balance in various diseases.

7. Discussion and future perspective

In recent years, epigenetic pathways have emerged as a key means by which gut microbiota communicates with the host immune system (8). Specifically, microbial metabolites SCFAs are regarded as key epigenetic regulators that induce local and systemic immunomodulatory activities through HDAC inhibition and associated histone acetylation. The present review provides valuable insights into the role of SCFAs as HDACi in the host immune system, highlighting their potential functions in immune cell and systemic protection. It is well-established that SCFAs exhibit targeted inhibitory effects on class I and II HDACs. Subsequently, they affect the tissue immune homeostasis both inside and outside the gut by regulating cellular immune activities. A substantial portion of these effects can be attributed to the direct regulatory actions of SCFAs on various immune cells. The present review initially concentrates on elucidating how SCFAs, through HDAC inhibition, regulate the cellular activities and functions of innate immune cells, including macrophages, DCs, neutrophils, MCs and NK cells, as well as T/B lymphocytes. These discoveries aid in the understanding, at the immune cell level, of the molecular pathways by which SCFAs promote histone acetylation modification and regulate host immunity via HDAC inhibition. Building on this, the present review proceeds to summarize the protective effects of SCFAs in both the intestine and extra-intestinal organs, thereby emphasizing the systemic immunomodulatory activities of SCFAs based on HDAC inhibition. Collectively, these aspects contribute to a profound understanding, from the

Table VI. Potential therapeutic effects of SCFAs as HDACi in other diseases.

Authors, year	Groups	Disease models	Therapeutic effects	Associated cells	Associated acetylation	Associated HDACs	(Refs.)
Chen *et al*, 2024	SCFAs	HFD-induced gestational diabetes mellitus	Elevate lipid transportation	IECs	H3K27 acetylation	Inhibit HDAC3 to reduce CD36 expression	(169)
Chen *et al*, 2024	Butyrate	Acute leptospirosis	Promote the bactericidal activity of macrophages	Macrophages	Unprovided	Inhibit HDAC3 to promote ROS production	(35)
Jiang *et al*, 2024		Chronic obstructive pulmonary disease	Suppress ILC2-dependent airway inflammation	ILC2 cells	NFIL3 promoter acetylation	Unprovided	(170)
Whitt *et al*, 2018		HFD-induced obesity	Reduce body weight and improve metabolic profile	IECs	Unprovided	Inhibit HDAC3	(171)
Islam *et al*, 2022		Ovalbumin-induced allergic asthma	Ameliorate airway inflammation and fibrosis	Unprovided	Histone H3K9 acetylation	Inhibit HDAC1	(172)
Olaniyi *et al*, 2024	Acetate	Letrozole-induced polycystic ovarian syndrome	Reverse cardiac energy depletion and attendant cardiomorbidities	Unprovided	Unprovided	Inhibit HDAC2/mTOR	(173)
Olaniyi *et al*, 2020		STZ-NA-induced diabetes mellitus	Rectify cardiac metabolic disturbance	Unprovided	Unprovided	Inhibit HDAC	(174)
Du *et al*, 2022	Propionate	Experimental autoimmune prostatitis	Ameliorate the prostatic inflammation and restore Th17/Treg imbalance	T cells (Th17/Treg cells)	Unprovided	Inhibit HDAC6	(175)

SCFAs, short chain fatty acids; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; HFD, high-fat diet; STZ, streptozotocin; NA, nicotinamide; ILC2, group 2 innate lymphoid cells; IECs, intestinal epithelial cells; NFIL3, nuclear factor interleukin 3; ROS, reactive oxygen species; mTOR, mammalian target of rapamycin.

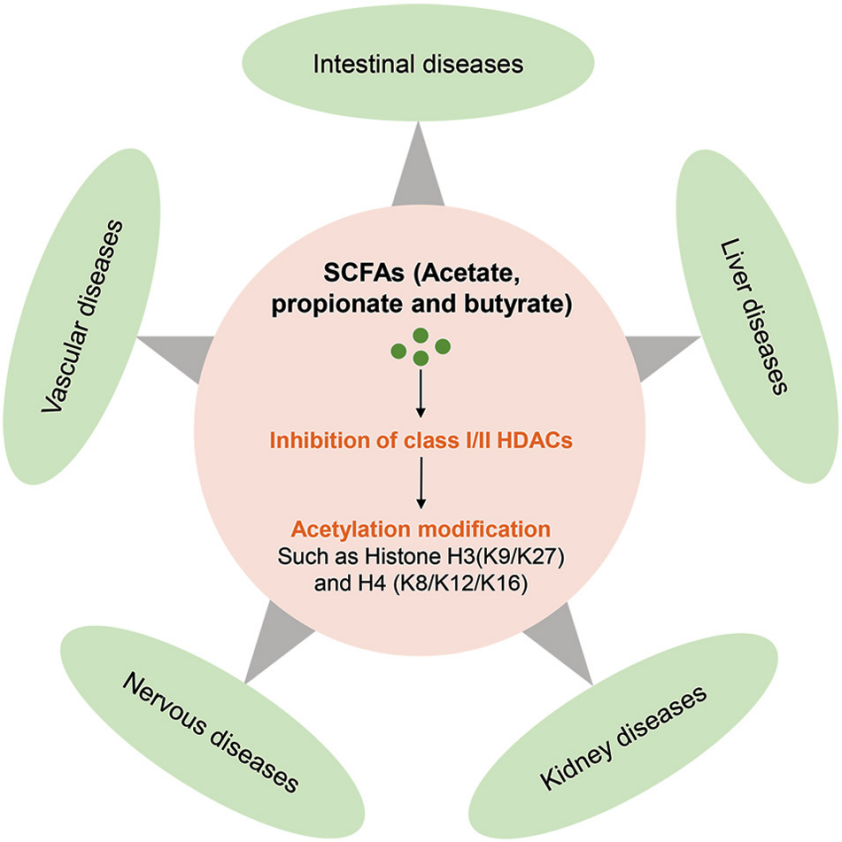

Figure 7. Therapeutic activities of SCFAs against various diseases based on HDAC inhibition and acetylation modification. SCFAs, namely acetate, propionate and butyrate, can exert a wide array of therapeutic activities against diseases of the intestine, liver, kidney, nervous system and blood vessels. Their underlying mechanisms are associated with the inhibition of class I/II HDACs activities and the regulation of acetylation modifications on histone H3 (K9/K27) and H4 (K8/K12/K16). SCFAs, short chain fatty acids; HDACs, histone deacetylase.

perspective of HDAC inhibition, of the important contribution of SCFAs as microbial epigenetic regulators to the host immune balance.

Epigenetic modifications wield a substantial influence over chromatin alterations and gene expression. These modifications are reversible and subject to intervention by environmental factors. However, aberrant epigenetic modifications frequently lead to dysregulated gene expression, which is associated with the onset and progression of various human diseases. In particular, abnormal acetylation modifications mediated by HDACs are considered a key mechanism underlying numerous human diseases, including inflammatory diseases, neurological disorders, metabolic diseases and beyond (146,148,176). As previously discussed, microbial SCFAs are potent HDACi that possess both cellular and systemic immunomodulatory activities. Consequently, the present review also revisited the therapeutic activities of SCFAs based on HDAC inhibition in immune-related diseases both inside and outside the intestine. These findings suggest that SCFAs promote the inhibitory activities of class I and II HDACs and associated histone acetylation in various disease models, including those of the intestine, liver, kidney, nerves and blood vessels. This enables them to exert a wide range of therapeutic effects, encompassing anti-inflammatory, anti-fibrotic, vascular-protective and neuro-protective effects (151-175). These aspects underscore the potential of SCFAs as epigenetic therapeutic agents by acting as HDACi.

Revisiting the aforementioned content, it becomes readily apparent that the majority of current research focuses on the SCFAs acetate, propionate and butyrate, with the latter seemingly exhibiting a stronger HDAC-inhibiting effect compared with the former two. For instance, butyrate proves to be more efficacious than acetate and propionate in considerably reducing the activation and pro-inflammatory mediator levels of different immune cells, such as macrophages, neutrophils and MCs through HDACi-dependent pathways (39,57,61). These findings have also indicated that butyrate has a relatively broad inhibitory activity against class I and II HDACs and promotes histone acetylation, both at the levels of immune cells and systemic protection. Moreover, butyrate exhibits extensive HDAC-inhibiting activity in the treatment of various diseases both inside and outside the gut. This implies that butyrate may be a representative HDACi among SCFAs, carrying out a key role in regulating the host immune system and treating diseases. However, the mechanism by which butyrate, acting as an HDACi, mediates acetylation modifications to influence immune homeostasis both inside and outside the gut still lacks in-depth exploration. This is primarily because to the best of our knowledge, the potential mechanisms underlying the regulation of site-specific histone acetylation by butyrate and its connection to gene activity remain largely unknown. In addition to histones, HDACs can also regulate the acetylation of other substrates, including lysine residues and transcription factors, ultimately

affecting gene transcription outcomes (177). Therefore, butyrate may attain broad regulation of gene expression by targeting multiple sites to modulate histone acetylation. A large number of high-throughput sequencing technologies, such as single cell and spatial omics (including epigenomics, transcriptomics, proteomics and metabolomics) technologies, may enable more precise dynamic observation and correlation analysis of the regulatory mechanisms of butyrate in both temporal and spatial dimensions (178,179). The majority of evidence supporting butyrate as a potent HDACi primarily stems from the aforementioned findings such as animal and *in vitro* research, yet it has yet to provide reliable validation in human patients. This poses a challenge to the advancement of its epigenetic therapy. Human pharmacokinetic data indicate that orally administered butyrate is rapidly absorbed in the small intestine, rather than in the colon where the gut microbiota resides. Consequently, the pharmacological activity of oral butyrate may differ from, or even be limited compared with, that of butyrate originating from the colon. Exploiting an appropriate delivery system can markedly leverage the pharmacokinetics of butyrate and optimize its action mechanisms, thereby accelerating its development and clinical application (180). For instance, Gong *et al* (181 developed and implemented a synthetic living bacteria to deliver butyrate to the intestine, elucidating the key role of gut butyrate in preventing colitis and maintaining intestinal mucosal homeostasis through the inhibition of colonic HDAC3.

Moreover, it is important to note that propionate and acetate also exhibit specific HDAC-inhibiting effects. For example, propionate can reduce IL-17 production by intestinal γδT cell populations based on HDAC inhibition, thereby promoting the alleviation of intestinal inflammation (88). Among the SCFAs at human peripheral blood concentrations, only acetate can markedly induce the formation of NETs and its mechanism of action is related to both GPR43 and histone acetylation (55,56). These may be associated with the actual physiological concentrations of SCFAs. The colon generates 500-600 mM of SCFAs per day, with acetate, propionate and butyrate constituting the predominant portion (182). However, merely a minor proportion of SCFAs in the colon can be absorbed into the systemic circulation. The concentrations of acetate, propionate and butyrate in plasma are detected as 25-250 μM, 1.4-13.4 μM and 0.5-14.2 μM, respectively (182). Additionally, the tissue uptake capacity can also affect the *in vivo* concentrations of SCFAs. For instance, within human brain tissues, the average concentration of butyrate stands at 17.0 pmol/mg, while the average concentration of propionate is 18.8 pmol/mg (182). Colonic administration of butyrate (100 mM; 60 ml) increases the release of butyrate in the human gut and its uptake by the liver, yet it does not affect the splanchnic butyrate release. This indicates that the liver metabolism can prevent an increase in systemic butyrate concentrations, further demonstrating that this dose of colonic SCFA administration is safe (183). Consequently, when exploring the systemic effects of SCFAs, the influence of their physiological concentrations cannot be disregarded. However, at present, the majority of preclinical studies have not given due attention to this issue. If deemed necessary, it is advisable to conduct investigations into the acetylation modification mechanism of microbial SCFAs as HDACi from the perspective of actual physiological concentrations. This approach will facilitate a more in-depth understanding of the immunomodulatory activities exhibited by different SCFAs. To sum up, systematically and thoroughly elucidating the acetylation mechanism by which SCFAs act as HDACi presents an exciting challenge. Achieving this will enable the attainment of a clearer understanding of the epigenetic regulatory activity of microbial SCFAs in the host immune system and provide novel insights for the treatment of human diseases.

8. Conclusion

In conclusion, the present review primarily elucidates the immune-regulatory roles of microbial metabolites, SCFAs, when acting as the HDACi. This is because SCFAs can extensively inhibit the activities of class I and II HDACs and promote histone acetylation, directly modulating the activation and functions of various immune cells, such as macrophages, DCs, neutrophils, MCs and NK cells. In parallel, a wealth of evidence indicates that through their HDAC-inhibiting properties, SCFAs can exert a variety of systemic protective effects. These effects extend beyond the local gut to encompass extra-intestinal organs, such as the liver, kidney, nerves and blood vessels. Given their HDAC inhibitory effects, SCFAs may serve as potential epigenetic regulators and carry out a key role in the treatment of multiple immune-related diseases within both the intestine and extra-intestinal regions. Among the SCFAs, butyrate emerges as a representative HDACi. However, the acetylation mechanism associated with the HDACi activity of SCFAs still requires in-depth investigation. This is essential to advance the understanding of their epigenetic regulatory activities in the host immune system and to facilitate the development of therapeutic approaches for various diseases.

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Competing interests

The authors declare that they have no competing interests.

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