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Immunomodulatory roles of microbiota-derived short-chain fatty acids in bacterial infections

Reza Ranjbar [a], Saeed Niazi Vahdati [b,*], Sara Tavakoli [c], Reza Khodaie [d], Hossein Behboudi [e,f]

[a] Molecular Biology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[b] Institute of Biochemistry and Biophysics, Department of Biochemistry, University of Tehran, Tehran, Iran
[c] Department of Biotechnology, Faculty of Biological Sciences, Alzahra University, Tehran, Iran
[d] Department of Biology, East Tehran Branch, Islamic Azad University, Tehran, Iran
[e] Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, Iran
[f] Institute of Biochemistry and Biophysics, Department of Biochemistry, University of Tehran, Shahid Beheshti University, Tehran, Iran

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ABSTRACT

In recent years, an overwhelming amount of evidence has positively recommended a significant role of microbiota in human health and disease. Microbiota also plays a crucial role in the initiation, preparation, and function of the host immune response. Recently, it has been shown that short-chain fatty acids (SCFAs) are the primary metabolites of the intestinal microbiota produced by anaerobic fermentation, which contributes to the host-pathogen interaction. SCFAs, such as propionate, acetate, and butyrate, are bacterial metabolites with immunomodulatory activity, and they are indispensable for the maintenance of homeostasis. Some evidence indicates that they are involved in the development of infections. In the present study, we provide the latest findings on the role of SCFAs in response to bacterial infections.

1. Introduction

Microbiota is a biological community of the commensal, symbiont, and pathogenic microorganisms, including bacteria, archaea, fungi, and viruses which are present across all eukaryotic organisms such as humans [1–4]. The microbiota has traditionally been used as a shield to pathogenic bacteria, generally referred to as colonization resistance [5]. The intestinal microbiota's complex functions must be organized between the millions of distinct bacterial organisms and the host [5]. This synchronization is accomplished by various chemicals varying from signaling molecules to metabolites [5]. The equilibrium between commensal and potentially pathogenic bacteria is essential to human health [6]. Microbiota supports the host by allowing the fermentation of non-digestible dietary components, such as complex sugars and lipid molecules [6]. The breakdown of this metabolite contributes to vitamin K development, the absorption of critical ions, and the improvement of essential cell function, such as regulating epithelial cell proliferation and differentiation [6]. Also, it has been found that the gut microbiota present in the digestive tract provides essential health benefits to its host, primarily through the regulation of immune homeostasis. In this way, mutual regulation between the immune system and microbiota is accomplished through several mechanisms, including the engagement of toll-like receptors (TLRs) and pathogen-specific receptors expressed on numerous cell types [7]. TLRs can identify ligands from commensal or pathogen microbiota to preserve the tolerance or trigger the immune response [7–9]. Besides, bacterial metabolites are also active in the modulation of immune system cell development [10,11].

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are among the essential metabolites synthesized by intestinal microbiota [12]. SCFAs, mainly butyrate, act as energy sources and induce neural and hormonal signals that control energy homeostasis [13]. In addition to their trophic impacts, they exhibit antioxidant, anticancer, and anti-inflammatory activity and play an essential role in maintaining digestive and immune homeostasis [14–16]. Intracellular SCFAs can block zinc-dependent histone deacetylases (HDAC1–11) [17] when entering the cells. HDACs are considered the epigenetic erasers, catalyzing histone deacetylation and contributing to the compaction of chromatin and transcriptional suppression [18]. In clinical trials, several HDACs have been evaluated, and a number of them have been successfully translated into the clinics. In addition to valproate, used as a mood stabilizer and anti-epileptic agent, vorinostat, romidepsin, and belinostat are prescribed to treat cutaneous and/or peripheral T-cell

* Corresponding author.
E-mail address: saeed.niazi.vahdati@gmail.com (S.N. Vahdati).

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lymphoma. Simultaneously, panobinostat is applied to cure patients with multiple myeloma who previously underwent romidepsin and panobinostat therapy [19]. Besides having powerful anti-inflammatory properties, a group of HDACs interfere with the development of innate immune responses, protect against lethal sepsis, and increase susceptibility to infection [20–24]. Regarding the anti-inflammatory properties of SCFAs, HDACs have been shown to increase vulnerability to infections in experimental studies and in patients involved in clinical oncology studies [25–30]; thus, a question may arise whether SCFA-mediated therapies are safe.

The aim of metabolomics studies is to target small molecule metabolites that affect the host metabolome and their biochemical purposes to investigate host-gut microbiota communications. Metabolome analysis defines the metabolites used for their biological consequences in intestinal host microbiota. [31]. Recent improvements in next-generation sequencing (NGS) have pointed to a revolution in advancing a culture-independent microbiota as well as an approach to distinguish gut microbial communities [32]. It is now indisputable that the gut microbiota profoundly influences the host immune system both within and outside the gut [32]. Aside from genetic factors, environmental factors play an essential role in shaping microbiota [32]. These factors should be handled with caution as improper practices such as overuse of antibiotics might boost disease risk by the microbiota-mediated immunomodulation. Based on these findings, microbiota-derived SCFAs provide a platform for the inhibition of pathogens. In summary, based on the outcomes for this article, SCFAs present a significant connection among microbiota, the host, and invasive enteric pathogens. Herein, we emphasized the role of acetate, propionate, and butyrate as typical SCFAs that have been documented to attenuate the immune reactions in response to bacterial infection.

2. Human gut microbiota

The human gut contains numerous colonies of a wide variety of microbes, comprising 10^{14} bacteria involved in various biological processes. This colonization begins at birth, forming a unique intestinal microbiota for each individual [33,34]. Currently, the characterization of gut microbiota has been dramatically enhanced due to the advent of novel approaches, such as NGS. In this regard, findings from the Human Microbiome Project (HMP), as well as the MetaHIT (META genomics of the Human Intestinal Tract), have provided a comprehensive vision of the human-associated bacterial community identified 2172 bacterial species collected from human beings. They are categorized into 12 various phyla, of which 93% belonged to Firmicutes, Proteobacteria, Bacteroidetes, and Actinobacteria [35,36]. It has been shown that 386 bacterial species are strictly anaerobic and found in mucosal regions, such as the gastrointestinal tract [36].

An extensive functional capacity of the human gut microbiota was recently identified. The existence of country-specific bacterial signatures was determined, showing that the composition of gut microbiota is shaped by different environmental factors, including diet and human genetics [35]. Nevertheless, it must also be said that different human microbiota compositions can share a degree of functional redundancy, yielding similar metabolite profiles [37]. These findings are significant for developing therapeutic approaches to alter and form the bacterial community in various diseases. A thousand taxonomic bacteria are condensed in a specific functional collective domain, the intestinal microbiota [38]. Like any other organ, the microbiota is associated with pathological and physiological processes, and individual health can be influenced when the composition of the human collective population is altered [38]. The therapeutics of bacteria-induced pathologies, such as microbiota transplantation, are increasingly available, and it should be noted that the new medical specialties, microbiotalogy, and microbiomology are being born.

3. Microbiota-derived short-chain fatty acids

Regarding the relationship between microbiota and humans, the human body provides nutrients that bacteria need. In return, the bacteria help the human with the catabolism of indigestible carbohydrates and the formation of SCFAs, which are essential for several physiological pathways and regulating immune responses [33]. SCFAs are molecules with 1–6 carbons formed during the fermentation of carbohydrates by bacteria, of which acetic acid (acetate) (C2), propionic acid (propionate) (C3), and butyric acid (butyrate) (C4) are the most abundantly formed [39]. The microbiota's crucial action in creating SCFAs has been reported in germ-free (GF) mice [40]. Furthermore, proteins could also be used as a substrate for the formation of SCFAs by the gut bacteria during the metabolism of amino acids, forming fatty acids such as isovalerate and isobutyrate [41]. However, dietary carbohydrates that enter the host colonic lumen are the most significant substrate for many bacterial species that enhance the colonic formation of SCFAs [42]. These molecules are requisite for the host's intestinal homeostasis since they support balanced microbial dynamics by suppressing the growth of several bacterial species in low pH values [43]. SCFAs affect the immune system in the intestine of the host and different organs [43].

Regarding the metabolism of SCFAs, acetate is either directly synthesized from acetyl-CoA or through the Wood-Ljungdahl pathway with formate aid [44]. Also, propionate is produced through succinate and acrylate pathways through simple sugars as substrates in these reactions from lactic acid as a precursor [43]. Finally, butyrate is generated by classical pathways due to the acetoacetyl CoA reduction to butyryl CoA, then converted into butyrate by butyrate kinase and transbutyrylase [43,45]. SCFAs are transported to intestinal epithelial cells through active transport and simple diffusion processes. Also, acetate and propionate are absorbed by the blood and reached other organs.

In contrast, butyrate is the primary source of energy for epithelial cells [43,45]. The concentration of SCFAs in the human intestine ranges from 20 to 140 mM. It depends on the structure of intestinal bacteria, the absorption of SCFAs from the intestine, and the contents of fibers in the diet [46].

4. Short-chain fatty acids and their receptors

SCFAs have been shown to communicate with distinct receptors, such as G-protein-coupled receptors 41 and 43 (GPR41 and GPR43), also known as free fatty acid receptors 2 and 3 (FFAR-2 and FFAR-3), respectively [47,48]. FFARs are polypeptides with seven-transmembrane α-helix domains and belong to the GPCR family [48]. They can detect SCFAs and trigger signal transmission processes [43,48].

SCFAs stimulate four receptors in the human cell membranes, including GPR43, GPR41, GPR109a, and OR51E2 [49]. In this regard, GPR43 is usually activated by propionic, acetic, and butyrate. Notably, butyrate and propionate have a high ability to stimulate GPR41 [50]. Butyrate and β-hydroxybutyrate can activate the GPR109a receptor, while acetate and propionate are considered the stimulators of the Olfr-78 receptor [43,51]. Additionally, SCFAs play a role in the activation of peroxisome proliferator-activated receptors γ (PPARγ) as well as the stimulation of the production of angiopoietin-like protein 4 (ANGPTL4/FIAF), involved in regulating lipid metabolism in gut bacteria and accumulation of the adipose tissue in the intestinal adenocarcinoma [52,53].

GPR43 is mainly expressed on gut epithelial cells, adipocytes, and immune cells [50]. Besides, GPR41 is expressed on multiple human cells, including the lymph node cells, adipocytes, splenocytes, large intestinal lamina propria cells, bone marrow cells, peripheral nervous system, and polymorphonuclear leukocytes [50]. GPR109a is expressed on the host and immune cells residing in intestinal epithelial cells, including dendritic cells, macrophages, monocytes, neutrophils [50,54].

5. Microbiota short-chain fatty acids and immunomodulatory roles

Microbiota-derived SCFAs apply their influence on host cells by various mechanisms, including 1) the activation of cellular receptors, resulting in cell differentiation and proliferation, 2) affecting the host cell metabolism by the production of metabolites within the cells, 3) acting as inhibitors of HDACs [43,55].

SCFAs are considered mediators in the interaction between the intestinal microbiome and the immune system (Fig. 1) [43]. The signal generating by them is transported to immune cells via FFARs, which relate to the family of GPCRs [43]. It has also been established that SCFAs hinder the activity of HDAC translational modifications, particularly the process of deacetylation and, what is new, the process of histone crotonylation [43]. These characteristics of SCFAs affect their immunomodulatory potential, i.e., keeping the anti/pro-inflammatory balance [43]. SCFAs attach to GPCRs, such as GPR41, GPR43, and GPR109A, expressing on the epithelial cells and immune cell surface [46]. The process of transport or diffusion of SCFAs within host cells occurs in their metabolism and/or hindrance of HDAC activity [46]. The influence of SCFAs on enhanced epithelial barrier function and immune tolerance is complex and promotes gut homeostasis through multiple mechanisms, namely enhanced generation of mucus by intestinal goblet cells, the repression of nuclear factor-κB (NF-κB), the activation of inflammasomes, the generation of interleukin-18 (IL-18); augmented discharge of secretory IgA (sIgA) by B cells, decreasing the expression of T cell-activating molecules on antigen-presenting cells, such as dendritic cells (DCs); and increasing the number and function of colonic regulatory T (Treg) cells, including the expression of FOXP3 and generation of anti-inflammatory cytokines (transforming growth factor-β (TGFβ) and interleukin 10 (IL-10)) [46].

A study performed by Astakhova et al. [47] found how SCFAs affect the signaling transduction pathway in lymphoid (Epstein-Barr virus-positive) and cancerous epithelial cells. They showed that butyrate induced the expression of interleukin-6 (IL-6) and interleukin-8 (IL-8), and these interleukins could enhance the activity of NF-κB in these human cell lines [55]. Furthermore, SCFAs can activate the early lytic phase of the Epstein-Barr virus (EBV) [55]. More importantly, butyrate contributes to the induction of apoptosis in cancerous lymphoid cells [55]. Astakhova et al. [55] found that carrier proteins, such as monocarboxylate transporter 1 (MCT1) and monocarboxylate transporter 4 (MCT4), are crucial for the penetration and activity of SCFAs into host cells [55]. These findings propose that SCFAs can affect the transport actions of host cells and participate in the removal of EBV-infected and

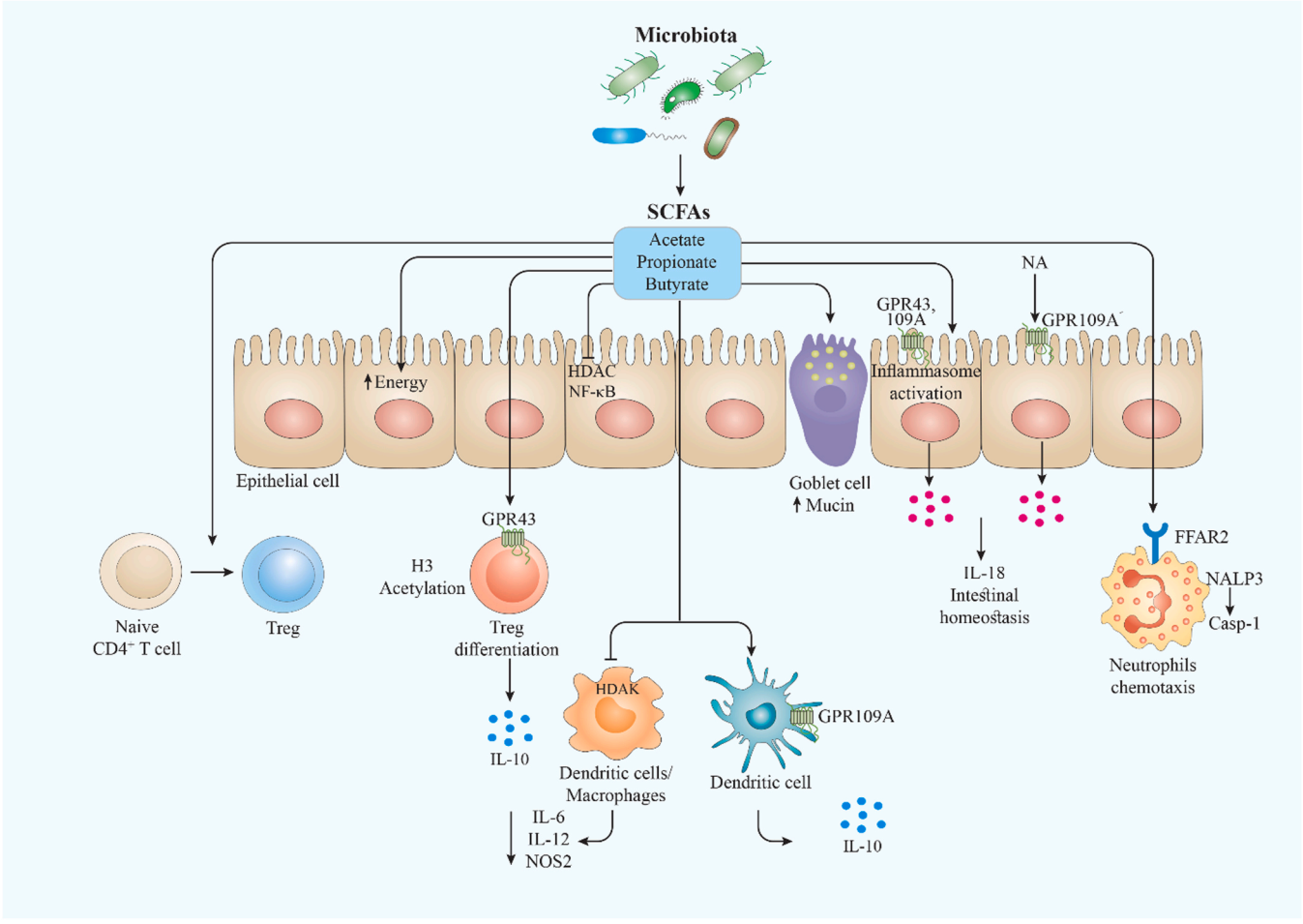

Fig. 1. The immunomodulatory role of short-chain fatty acids in the immune response. Metabolites derived from microbiota (including acetate, propionate, and butyrate) are associated with shaping the mucosal immunity. These metabolites participate in a complicated host-microbiome network of interactions that organize the immune response. The most well-studied metabolites SCFA and NA, are proposed to influence many aspects of the immune response, including DC and macrophage function, cytokine release, Treg differentiation, the mucin discharge from intestinal goblet cells, inflammasome-mediated IL-18 activation, and neutrophil chemotaxis via the NF-kB pathway. Also, in neutrophils, acetate-FFAR2 signaling stimulates their recruitment to the inflammatory situations, promotes inflammasome activation, and increases the secretion of IL-1β, while in ILC3s, acetate-FFAR2 enhances the expression of the IL-1 receptor, which promotes IL-22 discharge in response to IL-1β. NA: Nicotinic Acid; HDAC: Histone Deacetylase; NOS2,: Nitric Oxide Synthase 2; SCFA: Short-chain fatty acid; FFAR2: Free fatty acid receptor 2; NLRP3: NLR family pyrin domain containing 3; Casp-1: Caspase-1; NF-κB: Nuclear factor-kappa B.

cancerous cells [55].

It has been found that SCFAs enhance the differentiation of T lymphocytes towards effector T and T-regs lymphocytes by inhibiting HDACs [56]. In this regard, the kinase pathway of the mechanistic target of rapamycin (mTOR)-S6K is imperative for the differentiation of T lymphocytes and the inhibition of HDACs in T lymphocytes by acetate. Propionate is capable of increasing the phosphorylation of the ribosomal protein S6 (the main target of the mTOR pathway) that influences the expression of interferon-gamma (IFNγ), IL-10, and interleukin 17 (IL-17) [56]. A study conducted by Park and colleagues [48] revealed that acetate could regulate the proliferation of T lymphocytes, controlled by cytokines and immunological factors. In this context, the populations of IL-10-producing T lymphocytes were enhanced by SCFAs.

In contrast, given stimulating the immune reaction, acetate promotes the effector T lymphocytes [56]. This situation is crucial because the formation of IL-10 by effector T lymphocytes determines their anti-inflammatory ability, which is significant in the weakness of immune reactions in inflammatory disorders [56]. Park et al. [56] also showed that propionate is able to stimulate the differentiation of Treg cells and the expression of Foxp3 (forkhead box P3) [43,56].

Additionally, it has been demonstrated that acetate and propionate can induce the differentiation of naive T lymphocytes towards T helper 17 (Th17) cells and incite the expansion of T helper type 1 (Th1) cells via interleukin 12 (IL-12) [43,56]. Th17 and Th1 lymphocytes are involved in immune reactions against microbial pathogens and inflammatory responses [56].

6. Microbiota short-chain fatty acids and bacterial infections

Intestinal microbiota facilitates mucosal barrier activity and improves the immune response to prevent enteric infection [57]. Interleukin-1 beta (IL-1β) is typically a cytokine throughout active infection essential for mobilizing neutrophils and eliminating pathogens [57]. The microbiota plays a crucial role in developing homeostatic pro-IL-1β concentrations in residential intestinal macrophages, such as myeloid differentiation-dependent primary response 88 (MYD88). The priming macrophages quickly respond to enteric infection by transforming pro-IL-1β to mature active IL-1β [58]. Intestinal microbiota may even improve host immunity by MyD88-independent mechanisms [57].

It has been shown that bacterial dysbiosis results in immune-mediated diseases and microbial infections [59]. Commensal bacteria are directly related to the surface of mucosal layers, causing complex interactions to achieve homeostasis of immune reactions and pathogen clearance [59–61]. In this regard, such interaction would be needed for effective immune responses without excessive inflammatory responses. Hence, resident commensal bacteria hold a continuous relationship with mucosal surfaces, resulting in mucosal immunity, tolerance, and inflammation in the human gut [59,62,63]. For instance, glycosylation of proteins in epithelial cells is mediated by commensal bacteria and group 3 innate lymphoid cells (ILC3s), regulating commensal host symbiosis and anti-bacterial host reactions [64,65]. T lymphocytes, innate immune cells, and immunoglobulin A (IgA) reactions also play significant roles in these mechanisms [64,65]. Commensal microbiota has been shown to direct intestinal Th17 and Treg cells [66–68]. It has been indicated that microbiota-derived SCFAs stimulate the formation of FOXP3 in CD4 + T lymphocytes and enhance the activity of Foxp3+ T regs cells producing IL-10 in lamina propria of the human intestine [69,70]. Of note, the anti-inflammatory effects of SCFAs are mediated via the inhibition of the activity of HDACs [71]. Based on this fact, chemical inhibitors of HDACs promote the function of Treg cells and have a beneficial impact on various disorders, such as autoimmune disease [72,73].

Microbiota-derived SCFAs can modulate a variety of cellular processes, such as chemotaxis, gene expression, proliferation, apoptosis, and differentiation [74]. It has been shown that the stimulation of GPCRs, the inhibition of HDACs, and the activation of histone acetyltransferase are remarkably influenced by SCFAs [74]. However, SCFAs (acetate, propionate, and butyrate) can accelerate the infection process. Several studies conducted on the SCFA levels in sputum of patients with cystic fibrosis showed that SCFA-mediated mobilization and survival of neutrophils exacerbated inflammatory reactions and facilitated the development of *Pseudomonas aeruginosa* [75]. Therefore, the immunoregulatory activity of SCFAs relies on the context and type of cells [46]. The involvement of GPCRs (cell-specific and tissue-specific) and their complex metabolite-sensing capacities help the management of host inflammation by controlling the infection process or causing damages and sustaining homeostasis [46]. Overall, in this review article, we will present a precise and updated description of the influences of microbiota-derived SCFAs on bacterial infections, as well as the molecular mechanisms underlying these processes. To this aim, we will summarize the literature published about the role of microbiota-derived SCFAs in some bacterial infections (Table 1).

7. Butyrate

The interplay between the host and microbiota is crucial to maintain the host intestinal homeostasis [76]. Nevertheless, a disturbance in this process via bacteria dysbiosis and host defense against invasive bacterial species could cause chronic inflammation [76]. Currently, it has been found that macrophages being differentiated in response to microbiota-derived butyrate exhibit increased anti-microbial activity. Such activity can alter the metabolic activity of macrophages, enhance host defense associated with LC3, decrease mTOR kinase activity, and help the formation of anti-microbial peptides in the absence of pro-inflammatory cytokines [76]. Besides, it has been shown that butyrate induces the differentiation of monocytes into macrophages via the inhibition of HDAC3 [76]. It has been reported that butyrate administration activates the anti-microbial activity in macrophages in the host intestinal and enhances the resistance to enteropathogenic bacteria [76]. In a study performed by Schulthess et al. [76], they found that (1) improved intestinal butyrate can cause host defense without causing inflammation, and (2) the inhibition of HDAC3 is capable of inducing some selective functions in macrophages involved in the host defense against bacteria. Microbiota-derived SCFAs stimulate the activity of intestinal epithelial barriers and modulate the host immune reactions in mucosal layers [77]. In this regard, butyrate serves as an initial energy source for epithelial cells as the first line of host defense toward invading bacterial pathogens [77]. Also, butyrate modulates the turnover of stem cells in epithelial crypts in the host intestine. This metabolite also incites Treg lymphocytes in the host colon via inhibiting the activity of HDAC at the Foxp3 locus [78–80]. Besides, the exposure of peripheral blood mononuclear cells, including macrophages, neutrophils, and dendritic cells, to SCFAs, can inhibit inflammatory cytokine production [81,82]. In-vivo models of intestinal inflammation show that microbiota-derived butyrate can play immunomodulatory activity [80].

This can be relevant for immunopathological events since diminished rates of butyrate-forming bacterial species were detected in the gut as well as in fecal samples of patients with colorectal cancer (CRC) and inflammatory bowel disease (IBD) [83,84]. It has been demonstrated that tissue-resident and intestinal phagocytes act as barriers in the intestine for invading bacteria. Malfunctionality of this process has been attributed to the pathogenesis of IBD because deficient microbicidal reactions have been reported in monogenic and polygenic forms of IBD [76,85,86]. Intestinal macrophages, compared with other macrophages, are mainly replaced by blood circulating monocyte cells. Hence, these monocytes reach the gut and undergo their final differentiation in the intestinal lamina propria to achieve maturation and become highly phagocytic cells. These cells show bactericidal activity through different mechanisms, such as reactive oxygen species (ROS) derived from nicotinamide adenine dinucleotide phosphate (NADP) oxidase, along with the formation of anti-microbial peptides [87,88]. However, microbial

Table 1
Immunomodulatory roles of short-chain fatty acids in bacterial infections.

Short Chain Fatty Acid	Bacterial infection	Function	Reference
Acetate	*Escherichia coli* O157:H7	The recent findings showed that acetate generated by probiotic bifidobacteria acts in vivo to promote defense (via inducing genes of ATP-binding-cassette-type carbohydrate transporter) and functions of the host epithelial cells and thereby defends the host from lethal infection such as *Escherichia coli O157:H7*.	[97]
Acetate	–	The generation of short-chain fatty acids (SCFAs), such as acetate, is a feature of symbiotic microorganisms, including *Lactobacillus casei* and *Bifidobacterium breve*, which are essential regulatory effectors of epithelial proliferation in the gut.	[131]
Acetate	*Clostridioides difficile*	Microbiota-derived acetate promotes innate host responses to *C. difficile* by impacting neutrophils and innate lymphoid cells (ILC3s).	[133]
Butyrate	–	(1) An increase in the level of intestinal butyrate may represent a novel approach to improve the host resistance without inducing tissue-damaging inflammatory responses, and (2) pharmacological interference of HDAC3 may contribute to discriminating macrophage roles in anti-microbial host protection.	[76]
Butyrate	–	Butyrate produced by resident skin microbes can prevent exaggerated inflammatory reactions by performing a down-regulatory role, sustaining a healthy state under physiological circumstances. SCFAs, such as butyrate, can be employed therapeutically to reduce inflammatory skin reactions.	[140]
Butyrate	*C. difficile*	Butyrate can protect the intestinal epithelial cells from the destruction induced by *C. difficile* toxins by stabilizing hypoxia-inducible factor 1 (HIF-1), attenuating the local inflammatory reactions and the systemic effects of infection.	[89]
Butyrate	*Mycobacterium tuberculosis*	Butyrate and propionate producers may significantly contribute to tuberculosis pathophysiology by boosting the anti-inflammatory reactions in the host.	[106]
Butyrate	*Citrobacter rodentium*	Butyrate supplementation at high levels modifies enteric bacterial populations and decreases inflammation of the intestinal tract in mice infected with *C. rodentium*.	[141]
Propionate	–	Propionate levels can precisely temper lung immune reactions in vitro and in vivo, and gut microbiome enhanced generation of propionate is correlated with decreased lung inflammation.	[124]
Propionate	*Listeria monocytogenes*	It has been appreciated that propionate may increase the antimicrobial actions of macrophages to limit the growth of intracellular pathogens such as L. *monocytogenes*. In this regard that propionate treated Macrophages are more restrictive to L. *monocytogenes* intracellular growth. Also, it has been discovered that propionate-treated macrophages have diminished numbers of L. *monocytogenes* in their phagosomes.	[123]

pathways that form the host defense of intestine macrophages are poorly understood. Thus, Schulthess and colleagues [76] evaluated the impact of microbiota-derived SCFAs on the function of macrophages. They found that SCFAs stimulate transcriptional and metabolic shifts in macrophages, which increase their bactericidal properties [76]. Schulthess et al. [76] indicated a role for butyrate as a differentiating agent in macrophages derived from monocytes. They also revealed that butyrate increases the intrinsic anti-microbial activity [76]. They also indicated that butyrate acts as an inhibitory factor in altering the metabolism of HDAC3 and can activate the production of anti-microbial peptides to increase bactericidal activity [76].

Currently, it has been found that the number of SCFAs-producing bacteria and the levels of SCFAs are significantly diminished in the intestine of patients infected with *Clostridioides difficile* [89,90]. Furthermore, it has been found that mice genetically susceptible to *C. difficile* infection have lower levels of SCFAs in their intestines. In a study carried out by Fachi et al. [89], they investigated the effects of butyrate on a murine model of acute *C. difficile* infection. It was shown that *C. difficile* infection is a proper case for the analysis of the host-microbiota interaction. They demonstrated that the disturbance in microbiota structure results in the susceptibility of mice to colonization and growth of *C. difficile* [89,91]. Studies showed that decreased host intestinal levels of SCFAs are caused by antibiotic therapy and increases the susceptibility of the host to *C. difficile* infection [90,92]. Fachi et al. [89] found that the restoration of intestinal levels of butyrate reduced the colonization of *C. difficile* in-vivo and showed that butyrate could be useful in attenuating and preventing the bacterial load of *C. difficile*. Besides, the use of dietary fibers and foods enriched with SCFAs-forming bacteria, such as Bifidobacterium, can reduce a load of *C. difficile* in the intestinal tract of the host [93,94]. Several lines of evidence demonstrated that microbiota-derived SCFAs are able to diminish the duration and severity of intestinal bacterial infections, including Shigella, enterohemorrhagic *Escherichia coli*, and *Salmonella Typhimurium* [95–97]. Various molecular strategies and cellular components could be targeted, such as controlling the colonization of bacteria, inhibiting the formation of bacterial toxins, and activating the host-intestinal defense [95–97]. Fachi et al. [60] showed that butyrate administration exerts a protective effect on *C. difficile* infection by directly influencing the intestinal epithelial cells.

It has been found that macrophages play an essential role in the host immune reactions by stimulating the anti-bacterial activity against bacterial infections and bone remodeling via the alteration of phenotypic and phagocytic polarization. Butyrate contributes to some biological processes and exerts immunomodulatory, anti-inflammatory, anti-microbial properties. Therefore, the accumulation of butyrate in phagocytic macrophages could be a possible choice for the regulation of macrophage behavior in specific environments to enhance the anti-

bacterial and immunomodulatory effects in bone implants [98–105]. The emergence of implant-induced infections and insufficient bone tissue integration are among the complications that urged physicians to use immunomodulatory and anti-bacterial agents in implant materials. The artificial implants have been primarily applied in orthopedic fields; nevertheless, implant-associated infections are frequently reported in postsurgical procedures, failing implants and causing systemic diseases [103–105].

The modulation of immune cell activity in various conditions is significant for the management of bacterial infection and bone integration. A study performed by Yang et al. [103] showed that sodium butyrate was loaded onto 3D porous sulfonated polyetheretherketone to regulate immune reactions in different situations. They found that sodium butyrate-loaded sulfonated polyetheretherketone possesses a remarkable anti-bacterial potential, particularly in samples containing high sodium butyrate levels [103]. The phagocytic activity of macrophages is enhanced following the bacterial induction with a rise in sodium butyrate levels through the reactive oxygen species formation, which prompted the bactericidal ability in the implant infection [103]. Also, sodium butyrate-containing sulfonated polyetheretherketone can polarize macrophages to M2 phenotypes, effectively participating in bone regeneration and tissue repair [103]. The findings of Yang et al. [103] showed that the sulfonated polyetheretherketone-B2 group had better anti-bacterial infection ability and much bone production at the proximity of implants. Overall, they indicated that the administration of sodium butyrate-containing porous sulfonated polyetheretherketone regulates macrophage reactions, proposing a novel method for the design of implant materials with better bone repair and anti-bacterial activity [103].

Studies indicated that gut microbiota is involved in the modulation of host immunity and metabolism. A survey conducted by Maji et al. [98] evaluated the alteration of gut microbiota in pulmonary tuberculosis and healthy controls. They found that the colonization of Bifidobacterium and Prevotella was increased in healthy controls. In contrast, the number of propionates- and butyrate-forming bacteria, including Eubacterium, Faecalibacterium, Phascolarctobacterium, and Roseburia, was significantly increased in tuberculosis patients. Also, they showed a decreased ratio of Bacteroidetes to Firmicutes in tuberculosis patients, which can influence the concentration of SCFAs [106,107].

Additionally, accumulating evidence indicates the diminished vitamin and amino acid biosynthesis rates in the enriched metabolism of propionate and butyrate in tuberculosis patients [106]. Generally, the findings of Maji et al. [106] imply that bacterial dysbiosis plays a critical role in the pathophysiology of tuberculosis by increasing anti-inflammatory cytokines [106].

It has been documented that butyrate influences human health through its activity as an anti-inflammatory factor, mostly by suppressing Nuclear factor-κB (NF-κB) and IFN-γ [108,109]. The NF-κB signaling pathway is imperative for the induction of immune reactions against some microbial pathogens. It participates in the transcriptional modulation of some cytokine genes, such as tumor necrosis factor-alpha (TNF-α) [106]. It is now known that TNF-α and IFN-γ have significant activity in the control of *Mycobacterium tuberculosis* infection and are crucial for granuloma production [106]. Of note, patients with latent tuberculosis are prone to disease recurrence following the anti-TNF- α therapy [106]. Butyrate can independently increase the number of T-reg cells in the gut, limit the collateral damage of tissues due to powerful anti-microbial immune reactions, suppress pro-inflammatory T-cell responses in tuberculosis patients, and increase the expression of IL-10 leading to chronic infection [106,110]. Notably, microbiota-derived butyrate acts as a mediator of immune reactions against *M. tuberculosis* in patients with diabetes mellitus, affecting individuals' susceptibility to tuberculosis [111]. It has been suggested that *M. tuberculosis* can stimulate the formation of IL-10, resulting in the oppression of the immune reaction [112]. Henceforth, a sharp rise in butyrate rate may negatively influence host immune reactions against *M. tuberculosis* infection.

It is understood that sodium butyrate is an SCFA salt secreted by butyrate-producing bacteria in the intestinal tract [113]. It is highly comparable with Class I and Class II HDAC zinc-dependent enzymes, thus hindering the function of most Class I and Class II HDACs [114]. Similar to HDACi, sodium butyrate also affects the transcriptional activity of genes within the cells and controls different cell activity. A number of studies have shown that sodium butyrate can facilitate catheter production (LL37), one of the most effective anti-bacterial peptides [115]. LL37 is primarily produced by activated macrophages, monocytes, neutrophils, and epithelial cells. Besides, it has been stated that LL37 not only possesses anti-microbial, anti-toxic, and immune-regulatory activity but also participates in wound healing and neovascularisation. Previous studies have suggested that LL37 may be resistant to *M. tuberculosis* by selective targeting of *M. tuberculosis* bacilli and the modulation of host cell immune responses, such as autophagia activation [116]. Therefore, in a study, Zhang et al. [117] examined the effect of sodium butyrate on the immune system by contamination of the host cells with *M.Bovis*.

The purpose of their research was to reveal a possible role of sodium butyrate in the production of LL37 and the control of the signal transduction pathway of NF-κB in macrophages infected with *M. Bovis* [117]. Noticeably, it was observed that sodium butyrate effectively improved the expression of LL37 in macrophages infected with *M.Bovis* [117]. Besides, sodium butyrate significantly decreased the intracellular infectivity of *M.Bovis* in macrophages [117]. Also, therapy with sodium butyrate significantly reduced the pathogenicity of *M. Bovis* in mice [117]. These results suggest that sodium butyrate could be used as a potential therapeutic agent for the treatment of bovine tuberculosis.

The exposure of host cells to butyrate increases the production of globotriaosylceramide (Gb3), the Shiga toxin receptor, a cytotoxin typical to enterohemorrhagic E. Coli (EHEC) and Shigella [5], respectively. When mice are fed with a high-fiber diet, the resultant elevation in butyrate production of the microbiota is associated with severe pathology and faster mortality as a result of EHEC disease than mice fed with a low-fiber diet with lower gastrointestinal butyrate rates [118]. It is believed that lifestyle change can modify the content of microbiota. In line with the increase in butyrate production, the generation of Gb3 is enhanced in host cells by increasing the vulnerability to Shiga toxin.

Also, SCFAs indirectly influence pathogen invasion by preserving the integrity of the gastrointestinal tract and stimulating intestinal immunity [8]. For instance, high concentrations of butyrate defend Caco-2 cells from invading and translating *Campylobacter jejuni* by triggering cell differentiation [119]. Butyrate also strengthens the intestinal barrier by stimulating AMP-activated protein kinase (AMPK) in Caco-2 monolayer cells [120]. AMPK plays a vital function in the homeostasis of cellular resources and modulation of tension in cytoprotection [121]. Sufficient amounts of SCFAs contribute to stabilizing the epithelial cells and prompt the immune response, whereas higher concentrations of SCFAs are toxic [122].

8. Propionate

Propionate is a microbiota-derived SCFA with a wide variety of functions in the human body. Some investigations have also delineated the impact of this metabolite on immune cell modulation [123]. Weis et al. [123] used *Listeria monocytogenes* to evaluate the immunologic consequences of propionate [123]. L. *monocytogenes* is an intracellular bacterium that proliferates inside the immune cells, such as macrophages. Weis et al. [123] assessed the effect of propionate on infection susceptibility in cell culture conditions. They showed that upon the treatment of macrophages with propionate before and during infections, a significant reduction is detected in the proliferation of L. *monocytogenes* [123]. They also proposed that propionate can strengthen the anti-microbial activity of macrophages in limiting colonization of L. *monocytogenes* [123]. The use of inhibitors that specifically block the

anti-microbial activity in macrophages showed a particular anti-microbial mechanism in these cells, increasing following the presence of propionate. These findings provide insight into the effects of propionate on modulating the immune reaction mechanisms during pathogen-host interplays.

A study performed by Tian et al. [124] demonstrated the gut microbiota factors modulate and control immune homeostasis in the lung. They demonstrated that the levels of microbiota-derived SCFAs, particularly propionate, are capable of inhibiting pulmonary inflammation and immune reactions. Unexpectedly, they detected pro-inflammatory effects caused by microbiota-derived propionate and butyrate when cells exposed to lipopolysaccharide (LPS) [124]. Compared with controls, they found a significant rate of propionate in the antibiotic-treated group compared with the acetate-treated group [124]. In order to exhibit the anti-inflammatory potential of high-dose propionate, Tian et al. [124] pretreated the lung of mice with excessive levels of propionate, leading to an increased colonization rate of *Staphylococcus aureus* [124]. They detected a high percentage of propionate-forming Lachnospiraceae in mice with diminished lung inflammation [124]. Tian and colleagues [124] showed a gut-lung immune axis in which microbiota-derived SCFAs play a significant role in the pathology of the lung [124]. It has been found that germ-free mice usually have substantial differences in local and systemic physiology. Their immune reactions have different behavior in response to pathogens in the absence of gut commensal bacteria [124,125]. This fact denotes that circulating factors derived from the gut microbiota can modulate the immune reactions in the host [126].

In a study carried out by Jeong et al.[127], they evaluated the effect of SCFAs on the proliferation of *S. aureus*. They showed that sodium propionate inhibits the proliferation of *Methicillin-resistant S. aureus* (MRSA) and multidrug-resistant (MDR) *S. aureus* isolates [127]. Interestingly, only sodium propionate improved skin infection induced by MRSA. Besides, sodium propionate significantly lowered the load of bacteria, cytokine formation, and the weight value of abscesses by two folds [127]. Furthermore, the isolates of *S. aureus* deficient for lipoteichoic acid and teichoic wall acid were more susceptible to sodium propionate than the wild-type [127]. Overall, the findings of Jeong et al. [127] showed that sodium propionate enhanced the skin infection caused by MRSA by reducing the proliferation of *S. aureus*, proposing that this metabolite might be helpful as an alternative treatment for *S. aureus* infection [127].

Moreover, a report by You et al. [128] showed that *Bacteroides vulgatus*, a predominant genus of *Bacteroidetes phylum* in the gut of the mice, restricts *Vibrio cholerae* infection, a common human pathogen. The findings also indicate that commensal-derived metabolites are essential determinants of host susceptibility to *V. cholerae* invasion. The current research uncovers a novel microbiota-extrinsic therapy that triggers extreme cholera-like symptoms in adult mice that are typically fully immune. In addition, You et al. [128] have shown that a drastic change in the metabolic output profile is responsible for the impaired tolerance to infections in the host [128]. The inhibition of metabolites, such as propionic acid, has been demonstrated to suppress the development of *V. cholerae*. These results indicate that clindamycin-induced improvements in the host intestine are expressed in the metabolite stage. These significant changes in the metabolic profiles greatly influence the intestinal development of *V. cholerae*. This study emphasizes the importance of commensal-derived metabolites as a primary factor for host vulnerability to enteric infection.

9. Acetate

Microbiota-derived acetate is abundantly found in the colon of healthy individuals, and several intestinal bacteria can generate this metabolite via metabolizing carbohydrates [97]. In a study conducted by Fukuda et al. [89], they discovered that acetate has beneficial effects on the activity of host epithelial cells and showed a valuable role in increasing the rate of probiotics, which protect the host epithelial cells against bacterial infection [97].

The evaluation of bacterial mediators and signaling pathways that affect epithelial homeostasis and bacterial symbiosis are currently under investigation [129,130]. In this regard, to assess the bacterial influence on the differentiation, proliferation, and death of gut epithelial cells, Matsuki et al. [131] performed a study in which the epithelial cells were exposed to *Bifidobacterium breve* and *Lactobacillus casei* as bona fide symbionts. They previously [132] have found that L. *casei* caused significant down-regulation in the expression of pro-inflammatory mediators in Caco-2 cells stimulated by Shigella strains [132]. However, along with the immune modulation, Matsuki and colleagues [131] assessed the molecular mechanism of epithelial homeostasis in the maintenance of bacterial symbionts. They revealed that acetate and lactate act as potential initial effectors in the transcriptional repression of cyclin E1 and cyclin D1 genes [131]. The expression of cell cycle regulators by SCFAs, including p57, p19, as well as the transcriptional factor GATA-Binding Protein 2 (GATA2) (inhibiting the formation of cyclin proteins, such as cyclin D1 and decreases the cell differentiation), show that these symbionts have complicated relationships with the epithelium in which complex signaling pathways control the cell cycle and induce cell differentiation [131]. These findings are the basis for further in-vivo research, confirming the colonization of *B. breve* and L. *casei* in the gut that affects the epithelial homeostasis in the host.

It has been indicated that antibiotic-stimulated bacterial dysbiosis is a crucial predisposing agent for *C. difficile* infections, intestinal disorders with mild diarrhea, and pseudomembranous colitis [133]. Fachi et al. [133] determined the influence of microbiota-derived acetate on *C. difficile* in in-vivo models. They indicated that acetate administration is significantly helpful for the improvement of the disease [133]. They demonstrated that acetate increased the immune reactions via affecting ILC3s and neutrophils induced by FFAR2 [133]. The acetate-FFAR2 signaling pathway stimulates the recruitment of neutrophils toward inflammation zones, enhances inflammasome assembly, and increases the expression of IL-1β. In group 3 innate lymphoid cells, this signaling pathway enhances the formation of the interleukin-1 receptor (IL-1R), which increases the formation of IL-22 in collaboration with IL-1β [133]. Fachi et al. [133] found that gut microbiota-derived acetate increases the innate immune reactions against *C. difficile* via coordinating the activity of ILC3s neutrophils [133]. It has been establishing that gut microbiota are crucial for the inhibition and expansion of *C. difficile* [134,135]. Fachi et al. [133] showed the protective effects of microbiota on acetate formation via fermentation of fibers, stimulating the FFAR2 signaling pathway in ILC3s neutrophils and coordination of their protective activity [133]. Overall, microbiota-derived acetate can increase the activity of neutrophils and ILC3s via FFAR2, which prompts host innate inflammatory and repair reactions to *C. difficile* [133].

The structure of microbiota, which causes an increase in the amount of acetate, has been shown to protect against Shiga toxin-mediated disease [5]. In a deadly EHEC disease model, mice inhabited with some Bifidobacteria, which contribute to higher amounts of acetate in the intestine, have less disease severity than those infected with Bifidobacteria strains, resulting in lower amounts of acetate. Acetate-producing microbiota enhances the boundary capacity of the gastrointestinal tract and inhibits Shiga toxin from entering the bloodstream [136]. The structure and metabolism of microbiota are significant factors in assessing the vulnerability and evolution of infection and promising new goals for the prevention and treatment of enteric infections.

SCFAs also are essential for preserving mucosal immunity by improving the intestinal epithelial cell (IEC) barrier function [46]. In addition to SCFAs, epithelial cell goblet cells enhance the expression of their mucin genes and immunization of germ-free mice with SCFA-producing *Bacteroides thetaiotaomicron* or *Faecalibacterium prausnitzii*, mediating the differentiation of goblet cells and development of mucosa [137–139]. SCFAs change the close intersection permeability of

IECs [136]. Colonization of Bifidobacterium longum strain provides a high degree of acetate defense against the contamination of enteropathogenic E. Coli O157:H7, suggesting that SCFAs can reinforce the stability of IEC and hinder the translocation of dangerous toxins from the intestinal lumen to the bloodstream [136]. These findings collectively illustrate the function of microbial-derived SCFAs in attenuating humoral and cellular immune responses and preserving mucosal homeostasis.

10. Conclusion

In this study, we addressed recent findings of the function of SFACs in bacterial infections. In response to bacterial infection, SCFAs, as mentioned earlier, act as a link between microbiota and the immune response. As presented in Fig. 1, this communication is involved in various molecular pathways and cellular processes and is indispensable for the maintenance of intestinal homeostasis. Such communication also plays a pivotal role in disease progression. Despite the advancements in this area, some dimensions of this association remained uncertain and need to be explored in more depth, as evidenced by the contradictory findings reported in the literature. We believe that this thriving field of research will affect our insight into the mechanisms by which diet, microbiota, and other factors affect the immune system function and, subsequently, the development of inflammatory and bacterial infections. In this context, it is essential to remember that this awareness will open up possibilities for developing new and more successful therapy for common inflammatory diseases. Based on the literature outlined in this study, SCFAs provide an essential strategy for preventing pathogens.

Conversely, several pathogenic microorganisms have evolved to survive in the gastrointestinal gradient of SCFA. They have developed mechanisms to control the expression of the virulence factors that permit efficient colonization of the host. In conclusion, SCFAs provide a crucial connection among microbiota, the host, and invasive enteric pathogens. Studies indicate a tiny reflection of the microbiota's many biochemical mechanisms that cause well-being and illness. Future research that better describes the function of SCFA in complicated intestinal interactions will increase our capacity to track and mitigate food contamination and promote better gut health.

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Declaration of Competing Interest

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