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Review

Role of microbiota short-chain fatty acids in the pathogenesis of autoimmune diseases

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ABSTRACT

There is emerging evidence that microbiota and its metabolites play an important role in helath and diseases. In this regard, gut microbiota has been found as a crucial component that influences immune responses as well as immune-related disorders such as autoimmune diseases. Gut bacterial dysbiosis has been shown to cause disease and altered microbiota metabolite synthesis, leading to immunological and metabolic dysregulation. Of note, microbiota in the gut produce short-chain fatty acids (SCFAs) such as acetate, butyrate, and propionate, and remodeling in these microbiota metabolites has been linked to the pathophysiology of a number of autoimmune disorders such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, celiac disease, and systemic lupus erythematosus. In this review, we will address the most recent findings from the most noteworthy studies investigating the impact of microbiota SCFAs on various autoimmune diseases.

1. Introduction

Microorganisms are found on host-environment surfaces for instance the skin and mucosal barriers such as the genital, gastrointestinal, and respiratory tracts [1]. Among the areas mentioned, the gastrointestinal (GI) tract has the largest area of primary mucosa in any individual, and interacts with a considerable range of diverse antigens and microorganisms, instantly after birth it is occupied by bacteria, viruses, fungi, and archaea [2–4]. *Actinobacteria*, *Bacteroidetes*, *Firmicutes,* and *Proteobacteria* are the abundant bacteriaduring homeostasis in the GI tract of humans [5–9].

Alterations in immune reactions in the absence of flora bacteria in intestinal lymphatic tissues underline the relevance of the host microbiota [10]. Current documents has been shown that the interplays between the host microbiota and the host immune system are required to keep tissue homeostasis [11–15]. Indeed, disruption of the host microbiota balance, particularly in the gut, has been found in a variety of disorders, including inflammatory bowel disease (IBD) (Crohn's disease (CD)and ulcerative colitis (UC)) [16,17], metabolic syndromes (such as obesity)[18–22], cancer, liver disease, type 1 diabetes (T1D) [23–26], rheumatoid arthritis (RA) [13,27–29], and multiple sclerosis (MS) [30,31]. However, the precise action mechanism of microbiota effect in the human disease pathogenesis is not fully understood and has now become a major field of study. Furthermore, intestinal microbiota interacts directly with the mucosal regions, influencing intestinal epithelial permeability as well as inflammatory activity [32]. The interaction between the microbial community and the host is also facilitated by the microbiota's secreted metabolites. The formation of short-chain fatty acids (SCFAs) by intestinal bacteria, for example, causes modulation of the host's mucosal immune response via several mechanisms, including the promotion of regulatory T cells (Treg) (Fig. 1) [32–34]. Our microbiota's composition is not fixed and is affected by a variety of factors like aging, geography, and numerous external factors such as diet and medication SCFAs [32–36]. This area's description and perception are one of the most dynamic fields of biomedical research, but it is still in its early stages. Several functions including the metabolism of amino acids, complex glycans, xenobiotics, and synthesis of SCFAs and vitamins can be attributed to the activity of microbiota [37]. Furthermore, the microbiota can counteract the activity of various pathogens such as *Shigella flexneri* and *Salmonella*, which can prevent inflammation caused

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by dysbiosis. In addition, abnormal microbiota can cause an inflammatory disease by microbes called pathobionts, and this condition is created in the host due to genetic predisposition and the use of antibiotics [7]. Because the host's immune system regulates microbial ecology, microbiota generates a variety of compounds like metabolites to influence immune system maturation and activity [38,39]. These metabolites are compounds that are generated by the host or the microbiota (for example, polyamines) or that are derived from the bacterial metabolism of dietary substances. Among the latter are aryl hydrocarbon receptor (AHR) ligands, polyamines, and SCFAs derived from undigested complex carbohydrates like butyrate, acetate, and propionate AHR [40]. AHR signaling is very important in maintaining immune homeostasis, and the protective function of AHR ligands toward mucosal inflammation through Interleukin (IL)− 22 synthesis has been demonstrated [41]. Polyamines induce the synthesis of intercellular junction proteins such as E-cadherin, zonula, occludins 1, and occludin, and as a result, they can fortify the intestinal epithelial cell barrier [42]. Additionly, they lead to the inhibition of innate immunity especially the activity of macrophages, inhibition of pro-inflammatory cytokine, and modulation of adaptive immunity. SCFAs have various roles including being an energy source for intestinal epithelial cells, and influencing the permeability of tight junctions [43]. As a result, the reinforcement of the epithelial barrier prevents the entry of toxic compounds into the bloodstream. Besides, as AHR activation, SCFAs also affect host immunity by mediating immune homeostasis and the development of Tregs through inhibition of histone deacetylases (HDAC) [44].

The primary SCFAs generated in the colon by bacterial fermentation of dietary fibers and resistant starch are acetate, propionate, and butyrate. In addition to the long-established importance of the colon in energy supply and trophic factors, as well as the control of Tregs, accumulating data suggests that SCFAs exert essential physiological effects on a number of organs.

A growing body of documents have found remodeling in the GI microbiota SCFAs associated with several disorders like T1D, MS, IBD, celiac disease (CeD), systemic lupus erythematosus (SLE), RA, Sjogren syndrome and thyroiditis diseases (such as graves and Hashimoto syndrome), among others. Hence, in this review, we will addresses, and discuss the role, and precise mechanisms through which these bacterial SCFAs have changed in autoimmune diseases.

2. Microbiota and immune system

The embryonic GI tract is thought to be sterile under normal circumstances, with the birth canal passage serving as the immune system's first contact with commensals [45]. The mucosal and systemic immune systems are thought to be shaped by these early contacts throughout time. While the process by which neonatal tissues overcome the daunting task of microbial colonization is still not fully known, it is thought that some of these early responses to commensals are defined by elements found in maternal milk. Indeed, living bacteria, metabolites, Immunoglobulin (Ig) A, immune cells, and cytokines are present in both colostrum and breast milk. Several elements work together to influence the microbiota of breastfed infants and how the host reacts to these microorganisms [45]. By binding nutritional and microbial antigens, maternal IgA, for example, limits immune activation and microbial attachment, while the presence of metabolites, such as oligosaccharides, in mother's milk encourages the proliferation of certain microbiota elements, such as *Bifidobacterium* [46,47]. It has been suggested that bacterially loaded dendritic cells in milk may contribute to neonatal immunological imprinting by affecting the kind of immune response to commensal antigens. Bacterial translocation from the mouse gut is enhanced during pregnancy and lactation [48].

The relative immaturity of the newborn immune system at birth and the tolerogenic milieu that characterizes early mammalian life may also

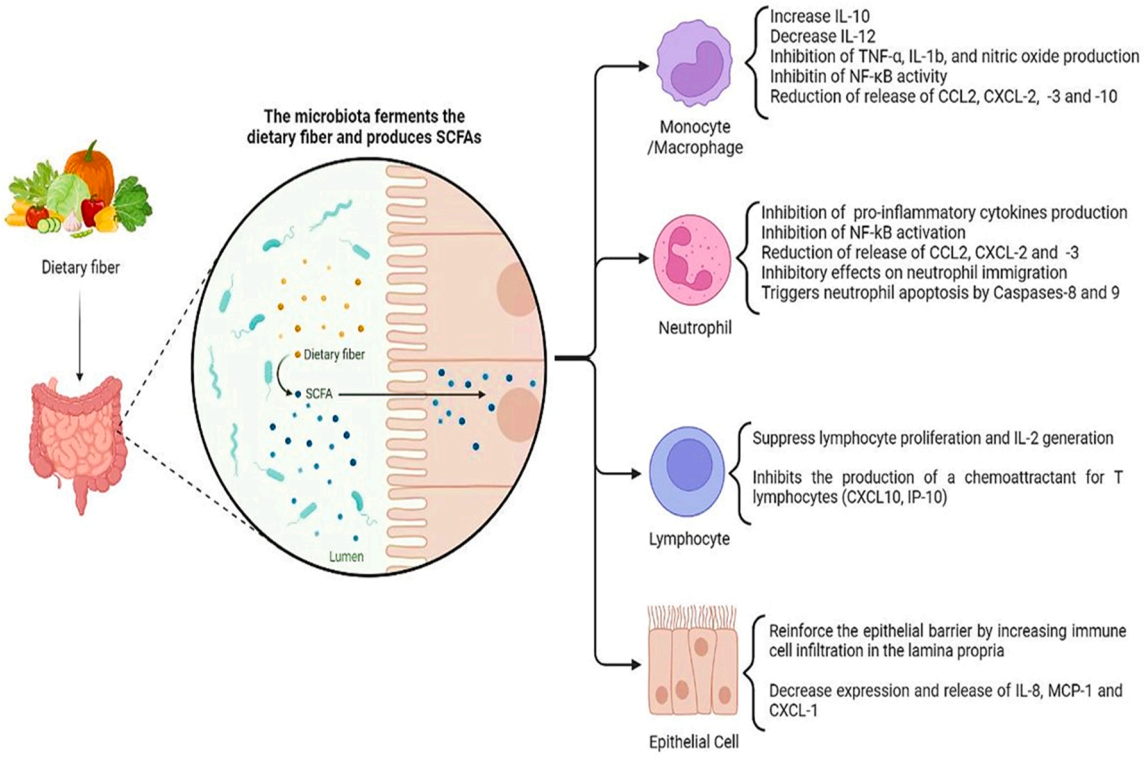

Fig. 1. Immunomodulatory role of SCFAs. As indicated in the figure, SCFAs have various functions and effects on epithelial cells and the immune system such as neutrophils, monocytes and lymphocytes in order to reduce inflammatory responses such as increasing the production and secretion of anti-inflammatory cytokines (IL-10) and inhibiting or reducing the production and secretion of inflammatory cytokines (IL-12, IL-1b and TNF-α) and chemokines (IL-8, CCL2, CXCL-1, −2, −3 and −10). SCFAs: Short chain fatty acids, TNF-α: Tumor necrosis factor-alfa.

be used to explain the ability to tolerate the microbiota. In fact, the immune system is still evolving, with inflammatory cytokine production being suppressed and T and B cell growth being directed toward regulatory responses [49]. High vulnerability to infections is a side effect of this dampened immune response, but this regulatory environment makes sure that the development of the microbiota takes place without overt inflammation. According to a recent study, a specific population of erythroid cells that are concentrated in newborns help to maintain this immunoregulatory milieu and reduce mucosal inflammation after the microbiota has colonized the area [50]. Early exposure to commensals may also suppress inflammatory response-inducing cells such invariant natural killer T (iNKT) cells, which has long-term effects on the host's ability to acquire inflammatory illnesses [51]. According to a recent study, this regulation may be achieved by early-life direct interactions between certain inhibitory commensal derived sphingolipids and iNKT cells [52].

The detection of conserved microbial related molecular patterns is one of the main mechanisms by which the host and the microbiota communicate with one another (MAMPs) [45]. To encourage a healthy microbial colonization, the neonatal innate immune system combines these signals in a special manner. Neonatal innate cells, for example, do express f Toll Like Receptors (TLR) ligands, but their response to microbial ligands differs from that of adult cells in that oxygen radical generation is noticeably reduced, while the synthesis of regulating cytokines like IL-10 is increased [53]. Part of this phenomena is caused by the activity of the microbiota. Early responses to microbial ligands, such as LPS, an endotoxin present in the outer membrane of gram negative bacterial walls, train gut epithelial cells to become hyporesponsive to later TLR activation [54,55]. While it is unknown how the innate immune system integrates microbial generated signals, new research suggests that epithelial cell production of epigenome altering enzymes may be essential for the coordination of commensal dependent intestinal homeostasis [56].

Commensals also aid in the post-natal development of the immune system, which aids in their containment. Germ-free mice bred in the absence of live microorganisms indicated that the microbiota plays a vital role in secondary and lymphoid structure development. This impact is most noticeable in the GI tract, where there are fewer Peyer's patches and fewer CD4 +T cells and IgA-producing plasma cells [57,58]. Tertiary lymphoid structures, such as isolated lymphoid follicles or crytopatches, are induced in the intestine after birth as a result of commensal exposure [59,60]. Commensals, as mentioned further below, may also contribute to the fortification of the intestinal barrier via a variety of processes, including the encouragement of epithelial cell maturation and angiogenesis [61,62].

When functioning correctly, the neonate immune system's highly regulated tone and the activity of commensals in the development and training of this system result in the construction of a long-lasting and homeostatic host/commensal relationship. These first interactions between the host immune system and the microbiota have far-reaching and long-term consequences for human health. Indeed, epidemiological studies have shown that changes in the microbiota of mothers or newborns may predispose to diseases associated with dysregulated barrier responses, such as asthma [63].

It is not unexpected that certain components of the gut microbiota have been associated to autoimmune illnesses, given their substantial influence on both the innate and adaptive immune systems. The involvement of gut bacteria in GI-related autoimmune disorders has received a lot of interest. Surprisingly, as previously indicated, the gut microbiota has an influence on several systemic immunological components in addition to the local gut immune system. As a result, current research has shed light on the role of gut bacteria in extraintestinal illnesses [64].

3. Pathogenesis of autoimmune diseases

Autoimmunity is defined by the reaction of immune cells such as T lymphocytes or immune system products such as antibodies against self-antigens (autoantigens). Immune responses against autoantigens may be physiological (natural autoimmunity) or pathological and lead to clinical manifestations called autoimmune diseases [65,66]. Various mechanisms can be involved in the induction and progression of pathological autoimmune diseases, the most important of which are genetic or acquired defects in tolerance or immune regulation pathways, disruption in the clearance of apoptotic cell substances, and molecular mimicry of viral or bacterial proteins [67,68].

The disease of autoimmune origin is usually chronic and irreversible, and its incidence is associated with genetic predisposition, and it is usually more common in women. Among the diagnostic symptoms of this category of diseases, it is possible to increase the level of immunoglobulins, especially specific autoantibodies, and the accumulation of lymphocytes and plasma cells in the wound place [65,66]. Some genes can cause an increase in susceptibility to autoimmune disorders like encoding histocompatibility molecules, peptide transporter proteins, and sex hormones that can independently increase the immunogenicity of autoantigens or by increasing their processing and presentation to macrophages and B lymphocytes to increase the chance of recognition by autoreactive B and T cells [65,69].

Autoimmune diseases may result from the predisposition to multiple interactions. In fact, an autoimmune disease occurs when there is an environmental trigger. As mentioned earlier, genetics is an important factor in the occurrence of autoimmune disease and constitutes about half of the risk of disease, but the other half is an environmental factor that causes the process to begin. Among the most dangerous triggers are microbial factors, especially factors that cause a chronic infection, diet, metal, toxins, radiation, and sex hormones such as estrogen, etc. In addition, nutritional deficiencies can also cause changes in the immune response [70,71]. For instance, protein-energy malnutrition and moderate deficiency of trace minerals (like zinc) and vitamins (especially A and D) cause impaired T-cell function, immunoglobulin A secretory response, phagocytic cell function, and decreased levels Several components of complement proteins are also seen following malnutrition [70,71].

The pathogenesis of autoimmune diseases is multifactorial, and in addition to genetic factors, other agents such as environmental and stochastic factors can be mentioned [72–77]. As mentioned, autoimmune diseases are usually caused by several factors, in which genetic and environmental abnormalities, along with disturbances in immune regulation processes, lead to the development of this category of diseases. In a healthy immune situation, several tolerance mechanisms like activation-induced death, anergy, and clonal insensitivity prevent the activation of autoreactive lymphocytes, but in autoimmune conditions, the survival and activity of autoreactive B and T cells increase in an encounter with autoantigen [66,78–80]. Nevertheless, in autoimmune disorders, defects in one or more tolerance mechanisms due to a combination of genetic factors such as Human leukocyte antigens (HLA) and non-HLA genes, various environmental factors like radiation, smoking, microbial agents, and disruption of immunoregulatory processes lead to the persistence of the autoreactive B and T cells and finally organ damage [79,81]. Immune regulatory abnormalities and an imbalance of inflammatory processes cause the development of autoimmune diseases. Extracellular vesicles, abnormal autoantigen scavenging machinery, pro-inflammatory and anti-inflammatory cytokine imbalance, antigen presentation, and defects in tolerance mechanisms are a few additional factors that could involves in the development and perpetuation of autoimmune processes and the progression of autoimmune diseases [82].

4. Microbiota in autoimmune diseases

The intestinal microbiota community, which contributes to normal growth and maintaining healthy human physiology, is one of the factors that have drawn attention in the last ten years. As demonstrated in models like germ-free mice, the microbiota not only controls various physiological functions of the body but also modulates and regulates growth and innate and adaptive immune function. [51,83,84]. For example, the microbiota plays an important role through nucleotide-binding and oligomerization domain-containing protein 2 and NLR family pyrin domain containing 6 (NLRP6) activity, both of which are arms of the innate immune system and essential for bacterial recognition [85,86]. Microbiota also causes the environmental differentiation of T helper (Th) cells, especially Treg and T helper 17 (Th17), so that some *Clostridia* species increase the number of Treg cells and segmented filamentous bacteria (SFB) lead to an increase in Th17 cells in mouse colon [29,87]. Some of the mechanisms mediated by bacteria that cause changes in immune function include [88] (A) metabolic products generated from food substrates, such as SCFAs, which act as regulators of innate and acquired immunity, and butyrate, which regulates the function of macrophages and induces the differentiation of Tregs[89,90]. (B) Some microbiota metabolites like the product of some strains of *Bacteroides fragilis* and polysaccharide A (PSA), have an immunomodulatory effect through TLR2. (C) Host metabolites modulated by the microbiota can influence the activity of immune proteins. In this regard, the bile acid component modulated by the microbiota can activate NLRP6 [85]. When the maintenance of homeostasis between the microbiota and the immune system is damaged, as a result of dysbiosis or dysfunction of the immune system, an uncontrolled inflammatory condition or breakdown of tolerance is created, which can lead to the initiation or promotion of autoimmunity [91]. There is body of documents that the gut, oral and skin microbiota act an important role in the pathogenesis of systemic and organ-specific autoimmune diseases.

5. Microbiota-derived short-chain fatty acids, their production, and functions

SCFAs are carboxylic acids with a shorter aliphatic tail of 6 carbons that are produced under anaerobic conditions by some species of bacteria from the fermentation of carbohydrates in the large intestine, though the liver is the primary site of natural production of these SCFAs [10,92]. Although dietary fibers, commonly known as prebiotics, is the major source of SCFAs, especially acetate (C2), propionate (C3), and butyrate (C4), other nutrients like proteins and peptides, can also be converted into SCFAs. Oligofructose, arabinoxylan, inulin, and pectin are fermented by bacteria and generate C2, C3, and C4 in large amounts (70–140 mM) in the proximal colon, and smaller amounts in the distal colon (20–70 mM) and distal ileum (20–40 mM) [93–96]. However, proportions could vary depending on factors like diet, microbiota composition, fermentation site, and host genotype [97]. The colonocytes primarily utilize butyrate, while the portal vein carries acetate and propionate to the liver. After being metabolized by hepatocytes, propionate either remains in the liver or is released systemically to the peripheral venous system. Hence, in peripheral blood, only acetate is usually detected [98]. According to earlier research, certain species with particular enzymes may be involved in the creation of the various SCFAs [99,100]. These enzymes also enable microorganisms to produce mono- and disaccharides from DF and other carbohydrates. Microbes make use of these saccharides to make SCFAs [101]. Reductive acetogenesis is the most common method of producing C2 by enteric and acetogenic bacteria. The oxygen-sensitive Wood–Ljungdahl pathway as an acetogenesis mechanism is regarded as the most efficient pathway of acetate formation by bacteria [101].

There are several pathways by which bacteria metabolize sugars to generate C3. These pathways include succinate, acrylate, and propanediol. Some *Bacteroidetes* and *Firmicutes* species prefer the succinate pathway [102]. There are two pathways for C4 production: C4 synthesis from acetoacetyl-CoA, which is formed by the reaction of two molecules of acetyl-CoA. Butyryl-CoA: acetate CoA-transferase converts butyryl-CoA to C4. Butyryl-CoA: acetate CoA-transferase is found in *Eubacterium, Roseburia*, *Anaerostipes*, and *Faecalibacterium prausnitzii*, and it extends acetyl-CoA to generate C4 [102,103]. Another route is by phosphotransbutyrylase and butyrate kinase. Certain *Coprococcus* species and numerous *Clostridium* species in the *Firmicutes* family, for example, have butyrate kinase to generate C4 [104].

SCFAs have broad physiological and immunological roles in the body. SCFAs have a local impact on the host enterocytes and digestive activity. For instance, butyrate as a major metabolic substrate for colonocytes provides at least 60–70% of the energy requirements necessary for colonic differentiation and proliferation [105]. Therefore, these cells are severely lacking in mitochondrial respiration, as evidenced by a decreased nicotinamide adenine dinucleotide (NAD+)/reduced NAD+ (NADH)ratio, ATP production, and oxidative phosphorylation, which can lead to autophagy. Donohoe et al. have shown that this deficit was corrected by adding butyrate to germ-free mouse colonocytes [106]. Besides providing energy to colonocytes, SCFAs in the gut influence colonic mobility, colonic blood flow, and PH of the GI environment, which affect electrolyte and nutrient absorption. Activation of G protein-coupled receptors (GPCRs) including GRP41, GRP43, and GRP109A could mediate these effects [107–110]. Butyrate affects human monocytes to increase IL-10 and decrease IL-12 production and in this way inhibits the production of proinflammatory molecules such as Tumour necrosis factor α (TNFα, IL-1b, and nitric oxide, and also Nuclear factor kappa B (NF-κB) activity [111]. Furthermore, butyrate inhibits the high mobility group box-1 and triggers neutrophil apoptosis by Caspases-8 and 9 activations [112]. Butyrate via an HDAC inhibitor-dependent or independent pathway can affect the different aspects of anticancer activity such as telomerase activation, GPR109a activation, expression of the butyrate transporter sodium-coupled monocarboxylate transporter-1(SMCT-1) − 1, and cancer cell apoptosis raising [113–116]. A wide spectrum of antimicrobial activity is associated with free fatty acids (i.e. medium-chain fatty acids and SCFAs). For example, propionate is used in food as an antimicrobial additive, and butyrate is used in agriculture to control *Salmonella* infections [117,118]. A study in human goblet-like cells line LS174T showed that butyrate and propionate can stimulate *Mucin 2 (MUC2)* expression and secretion. This suggests that SCFAs act as critical bacterial products for gut integrity [119].

6. The Role of SCFAs in the inflammatory responses

An inflammation condition such as pathogenic bacteria presence can be conducted through different inflammatory immune responses, such as immune cell chemotaxis, releasing of reactive oxygen species (ROS), and the formation of pro-inflammatory cytokines. There are some ways in which SCFAs affect immune responses. By influencing leukocyte chemotaxis, chemokine production, adhesion molecule expression, inflammatory molecule generation, and phagocytosis, SCFAs play a role in inflammation [120]. In non-inflammatory conditions, SCFAs stimulate the migration of neutrophils by activating GPR43 [121–123]. Leukocytes, for instance, neutrophils and monocytes, express GPR43, which pair with Gi/o and Gq proteins [108,121,123–125]. When agonists bind to this receptor, they activate several intracellular pathways including protein kinase C, mitogen-activated protein kinases (MAPKs), and transcription factors like activating transcriptional factor-2 (ATF-2) [122].

According to some evidence, SCFAs or phenylacetamide-1 elicit GPR43-dependent activation of Protein kinase B (PKB) and MAPKs (p38 and extracellular signal-regulated kinase (ERK)) through Gi proteins involvement in neutrophils [126]. In neutrophils, GPR43 agonists also activate Rac1/2 GTPases and phosphorylate ribosomal protein S6. Inhibiting PI3K, Rac2, p38, and ERK through genetic and

pharmaceutical interventions significantly lowers GPR43-dependent chemotaxis. These results demonstrate that neutrophils move in response to SCFAs via these signaling pathways [126]. Additionally, SCFAs can enter cells via passive diffusion to block the AMPK/mammalian target of rapamycin (mTOR) /mitochondrial pathway, HDAC, and MAPK pathway by enhancing MKP expression [127]. Further research is still necessary to determine whether SCFAs could also pass via the cell membrane through transporters in neutrophils, macrophages, and dendritic cells (DCs).

Despite the chemotactic role of SCFAs, there are some reports about their inhibitory effects on neutrophil immigration in inflammatory conditions. For example, in inflammatory conditions, phenylacetamide, a human GPR43 agonist, prevents the chemotaxis of neutrophils through C5a by mimicking GPR43 [121,124,125]. Under basal conditions, SCFAs might attract inflammatory cells due to their dual effects on chemotaxis. SCFAs may reinforce the epithelial barrier by increasing immune cell infiltration in the lamina propria. Normally, the immune system releases neutralizing IgA to induce content leakage from the gut; Studies have shown that butyrate via HDAC inhibition decreases telomerase activity [128]. SCFAs alter both the activity and migration of immune cells. Neutrophils' GPR43 is activated by acetate, which encourages the release of ROS [122]. ROS are powerful bactericidal elements that eliminate infections. In addition to their capacity to directly kill bacteria in the phagosome by inflicting oxidative damage on vital biomolecules, ROS can also activate phagocytes' pathogen defense mechanisms through a variety of non-oxidative mechanisms, including autophagy, receptor signaling, the formation of extracellular traps, and the direction of lymphocyte responses [129]. Of note, ROS control cytokine production during infection to coordinate the inflammatory process [130]. The antioxidant defense system of the cell regulates ROS generation [131]. The three superoxide dismutases SOD1, SOD2, and SOD3 catalyze the dismutation of O2 to H2O2, whereas catalase detoxifies H2O2 to H2O and O2 [132]. Although catalase is found in peroxisomes, cytosol, and mitochondria, the subtype-dependent compartmentalization of SODs is rather stringent [131]. SOD1 is found in the cytosol and intermembrane space of mitochondria, while SOD2 is found solely in the mitochondrial matrix and SOD3 is found primarily in the extracellular space. Several soluble components, including glutathione and thioredoxin, and membrane-integrated compounds, including -tocopherol and coenzyme Q, contribute to cellular antioxidant defense by scavenging ROS [131].

Under stable in vitro circumstances, butyrate metabolism by mitochondria creates modest quantities of reactive oxygen species, which indirectly block the nuclear transcription pathway via NF-ϰB [133]. However, the energy deficit seen in diversion colitis may result in oxidative stress and elevated ROS concentrations, which stimulate NF-ϰB signaling, DNA binding, and subsequent generation of inflammatory cytokines [134]. Modest increases in ROS induce the synthesis of another transcription factor, nuclear factor erythroid 2–related factor 2 (Nrf2), which translocates to the nucleus and binds to antioxidant response elements (ARE) on stress-responsive genes [134]. In response, Nrf2 binding to ARE activates genes involved in antioxidant and anti-inflammatory defense systems inside the cell. In an attempt to protect cells, excessive ROS concentrations and oxidative stress inhibit Nrf2 translocation and increase NF-ϰB signaling [134]. This concentration and duration impact of biological substances, such as ROS and signaling proteins, is suggestive of the duality of their possible activities and the significance of regulatory mechanisms required to maintain cell and tissue homeostasis.

Telomerase activity might serve as a target for butyrate-induced anticancer effects since it can support cancer cell proliferation. Butyrate (and to some extent acetate and propionate) can suppress lymphocyte proliferation and IL-2 generation in culture [135]. SCFAs influence neutrophils' synthesis of inflammatory mediators. Monocytes, macrophages, and lymphocytes are drawn to their chemokine. The release of CXCL-2 and − 3, also known as cytokine-induced neutrophil chemoattractant-2 (CINC-2), by neutrophils and macrophages after Lipopolysaccharide (LPS) stimulation is reduced by propionate and butyrate [126,136].

Cox et al. [137] discovered that in the presence or absence of LPS, SCFAs, butyrate being the most potent and acetate being the least, decrease macrophage chemoattractant protein-1 (MCP-1, also known as C-C Motif Chemokine Ligand 2 (CCL2)) production Butyrate influences the expression and release of IL-8, MCP-1, and growth-related oncogene (growth-related oncogene (GRO), also known as Chemokine (C-X-C motif) ligand 1 (CXCL1)) in intestinal epithelial cells in response to cytokines and microbial-derived compounds like peptidoglycan [138–140]. Butyrate inhibits the production of a chemoattractant for T lymphocytes and monocytes, interferon (IFN)-gamma-inducible protein-10 (IP-10) also known as C-X-C motif chemokine ligand 10 (CXCL10)) in human colonic subepithelial myofibroblasts [141]. SCFAs' chemokine-related activities may influence inflammatory and immunological responses in the GI tract. It has been found that propionate, butyrate, and acetate in order of potency, inhibit the activation of NF-kB on cancer cells and neutrophils stimulated by LPS [111,142], and induced apoptosis pathway through Caspase 8 and Caspase 9 activation [112]. Moreover, these compounds might inhibit high mobility group box-1 (HMGB-1), which is a nuclear transcription factor downstream of NF-kB [112].

A study performed by Säemann et al. [111] in 2000 reported that butyrate inhibited IL-12 production and increased IL-10 formation in human monocytes, and Ni et al. [143] in 2010 showed that butyrate suppressed the production of proinflammatory molecules IL-1b, TNF-α, and Nitric oxide (NO). All of these processes could reduce host injury while allowing both the host and the SCFA-producing bacteria to survive.

7. Role of microbiota SCFAs in autoimmune diseases

SCFAs, metabolites produced by gut microbiota have been looking for fermentation of indigestible carbohydrates like dietary fibers and resistant starch, which have immunomodulating effects. Studies have shown that SCFAs have enhanced anti-inflammatory effects, while long-chain fatty acids have pro-inflammatory effects [144,145]. The exact mechanism of function of microbiota SCFAs in inflammatory and autoimmune diseases is not clear and many studies have focused on various aspects of the function of these metabolites in this category of diseases [144–149]. In this section, we overview the information about the role and action mechanism of microbiota derived SCFAs in different autoimmune diseases (Table 1).

7.1. Diabetes

Microbiota SCFAs can influence diabetes. Both T1D and type 2 diabetes (T2D) can be involved. In T1D, insulin-producing beta (β) cells in the islets of Langerhans undergo autoimmune destruction [179]. SCFA has inflammatory and anti-inflammatory roles. SCFA causes immune cells such as macrophages and DCs to drive more T cells to become regulatory [89,180] and causes T cells to generate more anti-inflammatory cytokines like IL-10 [155]. In contrast, SCFA induces Th1 and Th17 against infection and another inflammatory process [181]. SCFA supports plasma cells to produce antibodies [182]. GPCRs and HDAC inhibition, regulates the functions of SCFA [183]. Free fatty acid receptor (FFAR) 2 and FFAR3 can recognize SCFA [184]. GPR43 (FFAR2) is activated by acetate, propionate, and SCFA therefore can induce cytokines such as IL6, and IL12 [185]. To improve the function of the intestinal barrier and ward off inflammatory disorders, GPR43 can be activated on intestinal epithelial cells [183]. T1D and the inhibition of autoimmune cells are most likely caused by these processes. Strong expression of GPR41 (FFAR3) and GPR43 is found in the pancreas, which is where T1D causes organ damage [186,187].

In non-obese diabetic (NOD) mice, a T1D model, it has been found a

Table 1
Role and mechanisms action of SCFAs in autoimmune diseases.

SCFA, and bacterial producer	Autoimmune disease	Study setting	Method of SCFA analysis	Mechanism	Effect on Immune responses	Function and conclusion	Reference
Acetate, butyrate, and propionate	Type 1 diabetes	*In vivo*	-	The gut microbiota of T1D patients stimulated distinct IgA-mediated immune responses compared to the gut microbiome of healthy controls. In NOD mice, treatment with the SCFA acetate lowered the IgA response elicited by gut bacteria and decreased the degree of insulitis.	IgA-related	The possibility that SCFAs might be used as possible therapeutic agents in the prevention and/or treatment of T1D. offers new insights into the functional impact of gut microbiota in triggering IgA immunological response in T1D.	[150]
Sodium butyrate	Type 1 diabetes	*In vivo*	Kaplan-Meier method	SCFAs inhibited intestinal proinflammatory responses caused by Kilham Rat Virus. SCFAs ultimately modified the B and T cell compartments in Peyer's patches.	Immune cells-related	The ability of SCFAs to alter the intestinal microbiota and stop virus-induced islet autoimmunity makes them potentially effective therapeutic agents for disease prevention.	[151]
Acetate, butyrate, and propionate	Type 2 diabetes	Clinical	Gas chromatography mass spectrometry System	In T2D patients, bile acids and bacteria that produce SCFA influence the mechanisms of lipid and glucose metabolism.	Metabolic-related	Production of SCFA can be to prevent or help to moderate T2D In patients with type 2 diabetes	[152]
SCFA of Clostridium clusters XI (Clostridium bifermentans), XIV (ASF 356 and 492) and XVII (C. ramosum) and the bacteroides species B. fragilis, as Clostridium cluster XIV members and B. fragilis	IBD	*In vivo*	Gas chromatography	By inhibiting adhesion molecules, chemokines, and neutrophil recruitment	Cytokines- and chemokine-related (Chemotaxis-related)	Protective role against inflammation (to increase Foxp3 + IL-10–producing cTregs and cTreg proliferative capacity, as well as to alter cTreg GPCR15 expression.)	[153]
Butyrate	IBD	*In vivo*	Flow cytometry and ELISA	Via GPR43, differentiated Th1 cells are induced to produce IL-10 by SCFAs, but HDAC is not inhibited.	Cytokine-related	SCFAs have the power to encourage Th1 cells and immature T-cells to produce IL-10.	[154]
Acetate propionate	IBD	*In vivo*	Flow cytometry real-time PCR ELISA	Activated the transcription of genes for IL-17A, IL-17 F, ROR, RORt, T-bet, and IFN-, which are associated with Th17 cells or Th1 cells. Direct inhibition of HDAC (HDAC) activity. It increased acetylation of p70 S6 kinase and phosphorylation of rS6, thereby regulating the mTOR pathway necessary for the generation of Th17 (T helper type 17), Th1, and IL-10 + T cells.	Cytokine-related, Immune cells-related	Depending on the cytokine environment, SCFAs may directly induce T-cell differentiation into T cells generating interleukin-17 (IL-17), interferon, and/or IL-10.	[155]
Butyrate	IBD	Clinical	Histologic parameters/ Immunohistochemistry/ Identifying humoral parameters/ Double-staining with antibodies	Butyrate therapy significantly decreased the number of macrophages with nuclear translocated NF-B positivity. In addition, butyrate dramatically decreased the amount of neutrophils in crypt and surface epithelia as well as lymphocytes/plasma cells in the lamina propria.	Immune cells-related	NF-ϰB translocation is reduced in lamina propria macrophages. The known anti-inflammatory effects of butyrate may partially be mediated by an inhibition of NF-B activation in these macrophages because the inflammatory process in UC is primarily maintained by macrophage-derive d cytokines.	[156]

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Table 1 (*continued*)

SCFA, and bacterial producer	Autoimmune disease	Study setting	Method of SCFA analysis	Mechanism	Effect on Immune responses	Function and conclusion	Reference
Propionate and butyrate	Bacterial metabolism in colon	C57BL/6 mice	Bone Marrow cells were flushed out/ Cultures/ Antibodies and Flow Cytometry/ Western Blotting/ RT-PCR	Altering the expression of particular transcription factors in DC precursor cells inhibits DC development.	Immune cells-related	It was found that SCFAs suppres immune function in the intestinal tract	[157]
SCFA/ high-fiber diet/ low-fiber diet	IBD	Mouse models of colitis	Western blots	These protective effects are mediated by SCFAs binding to the'metabolite-sensing' receptors GPR43 and GPR109A in non-hematopoietic cells. SCFAs binding to GPR43 on colonic epithelial cells increases K+ efflux and hyperpolarization, leading to activation of the NLRP3 inflammasome.	Metabolic-related	Although extremely high intakes of dietary fiber or the SCFA acetate prevent colitis, diets lacking or low in fiber increase the development of colitis.	[158]
Acetate, propionate, *i*-butyric acid, *n*-butyric acid, *i*-valeric acid, and *n*-valeric acid.	CD	Clinical	Microflora-associated characteristic (MAC)	-	-	These results demonstrate that the low total SCFAs concentration in this group of coeliacs is comparable to that in healthy controls.	[159]
Acetate propionate and butyrate	CD	Clinical	Gas chromatography	Alterations in the metabolic activity of the microbiome of the gut	Metabolic-related	The findings demonstrated that stool SCFAs concentrations were greater in CD patients and first-degree relatives than in healthy participants.	[160]
Butyrate propionate	HEK293 cells	Cell Culture	HDAC Assay	Incubation of HEK293 or HeLa epithelial cells with physiological concentrations of the SCFAs butyrate or propionate increased NF-B activation mediated by TLR5, TLR2/1, TLR4, and TLR9 agonists. SCFAs also boosted NF-B activation in response to TNF.	Signaling-related	These findings demonstrate how bacterial SCFAs quickly change the epigenetic state of host cells, redirecting the innate immune response and specifically reprogramming the production of cytokines and chemokines.	[161]
Butyrate- *Clostridia XIVa and IV clusters*	MS	*In vivo* – EAE mice	-	Increase Treg cells Decrease IFN- γ cytokine	Cytokine-related, Immune cells-related	Decrease inflammation	[162]
Butyrate-	MS	*In vivo* – EAE mice	-	Induce remyelination Enhance the maturation of oligodendrocytes	Immune cells-related	Ameliorate demyelination	[163]
Butyrate- *Clostridium tyrobutyricum* (CBut)	MS	*In vivo* – EAE mice	-	Improve the integrity of BBB and reduce the migration of immune cells to CNS	Cytokines- and chemokine-related (Chemotaxis-related)	Modulate BBB function	[164]
Propionate-	MS	*In vivo*- MS patients	-	Increase the number and function of Treg cells	Immune cells-related	Immunomodulatory effects	[165]
Acetate, Butyrate, Valeric acid, Isovaleric acid, Hexanoic acid, Octanoic acid, and Heptanoic acid– SCFAs-producing bacterial taxa from fecal samples of healthy donor	SLE	Pilot clinical trial	Gas chromatography-mass spectrometry	Decrease level of IL-6 Decrease CD4 + memory/naïve cells ratio	Cytokine-related, Immune cells-related	Anti-inflammatory effects	[166]
Butyrate and Propionate	SLE	*In vivo*- mouse lupus models	-	Modulate B cell activation and antibody production	Immune cells-related	Immunomodulatory effects	[167]
Propionate, Acetate, and Butyrate	SLE	*In vivo*- mouse lupus models	-	Downregulate type I IFN pathways	Signaling-related, Cytokine-related	Anti-inflammatory effects	[168]

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Table 1 (*continued*)

SCFA, and bacterial producer	Autoimmune disease	Study setting	Method of SCFA analysis	Mechanism	Effect on Immune responses	Function and conclusion	Reference
Propionate, Acetate, and Butyrate	SLE	*In vivo*-Lupus prone NZB/WF1 mice	-	Increase in Treg frequencies	Immune cells-related	Does not considerably improve the pathophysiology of lupus	[169]
Butyrate and Propionate	RA	*In vivo*--mouse RA models	-	Reduce osteoclast activities	Immune cells-related	Regulation of bone homeostasis	[170]
Butyrate	RA	*In vivo*--mouse RA models	-	Inhibit HDAC (HDAC)	Metabolic-related	Decrease inflammation	[171]
Acetate, Propionate, and Butyrate	RA	*In vivo*-RA patients	Gas chromatography-mass spectrometry	Decrease pro-inflammatory and pro-arthritogenic cytokines and chemokines levels such as IL-18, IL-33, and MCP-1	Cytokines- and chemokine-related (Chemotaxis-related)	Decrease inflammation and improve RA disease	[172]
Acetate, Propionate, and Butyrate	RA	*In vivo*-mouse RA models *In vitro*-	-	Inhibit arthritogenic fibroblast function Interfere production of inflammatory mediators, e.g. TNF-α, through Sf cells	Cytokine-related, Immune cells-related	Decrease inflammation	[173]
Butyrate	Sjogren syndrome	*In vivo*	-	Bbutyrate can alleviate Sjogren's syndrome via reciprocal modulation of IL-10 and IL-17-producing B cells.	Cytokine-related	This research identified the therapeutic effects of butyrate on an experimental animal model for Sjogren syndrome, as well as its effects on the balance of B cells via genes related to the circadian clock.	[174]
Butyrate	Primary Sjogren syndrome	Clinical-in vitro	Liquid gas chromatography-mass spectrometry	SCFAs, particularly butyrate, play a crucial role in immunity status, improving the gut mucosal immune barrier by boosting Treg cell activity and IL-10 production.	Cytokine-related, Immune cells-related	It was discovered that gut microbiota-related metabolites could be a new starting point for mechanistic study on Primary Sjogren syndrome and as a tool for early diagnosis, therapy, and prediction.	[175]
Acetate, propionate, butyrate, and valeric acid	Graves' disease	Clinical	Gas chromatography-mass spectrometry	Several hypothesized mechanisms, such as controlling the integrity of intercellular junctions and microbial transcriptomic, proteomic, and metabolic changes, suggest that altered microbiota composition in the gut and decreased microbial products, especially SCFAs, promote the development of autoimmune thyroid disease.	Metabolic-related	Our knowledge of how the probiotic *Bifidobacterium longum* controls the gut microbiota and lowers the recurrence rate in Graves' disease patients has been expanded by the current study. They have also developed a potential treatment for this condition based on the regulation of the intestinal microbiota.	[176]
Propionate and butyrate	Graves' disease	Clinical-in vitro	Gas chromatography-mass spectrometry	Along with other pathogenic variables, gut dysbiosis leads to a Treg/Th17 imbalance through the pathway mediated by propionic acid and promotes the development of GD.	Immune cells-related	This research illuminated the potential of microecological therapy as an adjunct therapy for Graves' disease and provided useful insights for improving immune dysfunction in Graves' disease patients using *B. fragilis*.	[177]
Bacteroides and, *Bifidobacterium* species	hashimoto thyroiditis	Clinical-in vitro	-	Nutrition may have had a significant influence in modifying gut microbiota	Immune cells-related, Signaling-related,	In this research, samples from individuals with Hashimoto thyroiditis showed a considerable rise	[178]

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Table 1 (*continued*)

SCFA, and bacterial producer	Autoimmune disease	Study setting	Method of SCFA analysis	Mechanism	Effect on Immune responses	Function and conclusion	Reference
				in Hashimoto thyroiditis patients.	Metabolic-related	in the *Bacteroides* species and a reduction in *Bifidobacterium*. Furthermore, it showed that enterocytes use SCFAs, products from anaerobic microbial fermentation, as a source of energy. When combined with thyroid hormones, particularly T3, these effects increase the integrity of the epithelial barrier and stimulate enterocyte differentiation.	

decreased SCFAs [188]. The role of microbiota was also clearly found as normal mice were less susceptible to T1D than germ-free mice, indicating the important role of microbiota in suppressing T1D [188]. Autoantigens-specific CD4 and CD8 T cells lead to this autoimmunity and some SCFA's can decrease the amount of it as also B cells. The development of T1D was suppressed by bacterial transfer to NOD mice, shows that a change in bacterial composition is essential in SCFA-related protection from T1D [188]. With these descriptions, it has been seen that changes in intestinal bacterial composition can be related to the development of T1D in humans [189–191]. A work found that the gut microbiome was dramatically altered by treatment with SCFAs and protected LEW1. WR1 mice against virus-induced islet destruction [151].

T2D is a metabolic disorder that results in the exhaustion of pancreatic β cell function after insulin resistance, which reduces insulin production [192]. Various observations have shown that patients with T2D had intestinal dysbiosis [193–196]. Individuals with T2D are characterized by a decrease in SCFA- forming microbiota and SCFA abundance and intestinal barrier dysfunction [193,197] so the production of SCFA can be to prevent or help to moderate T2D In patients with T2D [198,199].

T2D patients had lower concentrations of butyrate-producing bacteria than control subjects did, including *Eubacterium rectal*, *Clostridiales* sp SS3/4, *Faecalibacterium prausnitzii*, *Roseburia inulinivorans* and *Roseburia intestinalis*. This demonstrates how butyrate plays a protective role in the pathophysiology of T2D [21]. SCFAs indirectly reduce appetite and food intake and prevent factors that can cause T2D. Because SCFAs can induce glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which increase the feeling of satiety. In addition, SCFAs can increase glycogen synthesis by reducing glycolysis and gluconeogenesis [200–202] and regulate blood glucose concentration through GLP-1 by increasing insulin secretion [203]. SCFAs also can induce amylin secretion by FFAR2 [204].

7.2. Inflammatory bowel disease

IBD is defined by chronic inflammation of the gut and is highly prevalent throughout the world. A range of factors can trigger IBD, which involves an unchecked immune response that results in chronic inflammation. IBD may be divided into two primary categories: UC, which impacts just the colon, and CD, which mostly involves the small intestine and colon. IBD patients may have an increase in effector cells as a result of increased cell adhesion ligands and chemoattractants inside the inflamed mucosa [205]. Some studies have found that SCFAs may serve a protective role against inflammation in vivo, particularly by inhibiting adhesion molecules, chemokines, and neutrophil recruitment when stimulated [153]. Through preserving the integrity of the epithelial barrier, encouraging B-cell IgA formation, and controlling T-cell differentiation, SCFAs have been demonstrated to preserve intestinal regulation. It has been shown that the immunosuppressive IL-10, which is produced by both T-effector and Treg cells, is essential for maintaining intestinal homeostasis and preventing IBD. IL-10 can inhibit intestinal inflammation through a variety of mechanisms [206]. It has been shown in one study that SCFAs stimulated GPR43-mediated formation of IL-10 by microbiota antigen-specific Th1. By inducing Th1 to generate IL-10, SCFAs reduced the pathogenic potential of gut microbiota antigen-specific Th1 cells in the generation of intestinal inflammation. In order to convert signals from SCFAs, GPCRs are primarily involved, including GPR41, GPR43, and GPR109 [206]. The GPR41 binds more effectively to SCFAs with long carbon chains, while the GPR43 binds better to acetate and propionate [153]. Butyrate and nicotinate most often activate GPR109a, whereas all types of SCFAs are capable of activating GPR41 and GPR43. The GPCR signaling pathway has been found to alleviate disorders that affect many other organsa, like cardiovascular, respiratory, and neurological systems [136,153]. It has been demonstrated that GPCR signaling has anti-inflammatory effects in many inflammatory diseases. A further advantage of the SCFAs is their extremely small size, which enables them to enter the nucleus directly and inhibit HDAC [155]. HDAC promotes gene transcription by preventing a process known as histone acetylation from tightening the chromatin structure of target genes [207]. SCFAs enhanced the production of the Signal transducer and activator of transcription 3 (STAT3) and mTOR-dependent transcription factor B lymphocyte-induced maturation protein-1 (Blimp-1) in Th1 cells via a different mechanism [208]. It is important that SCFAs promoted the production of IL-10 by T-cells from individuals, including IBD patients since it demonstrates that SCFAs offer a novel therapeutic potential for the treatment of IBD [208]. SCFA-producing bacteria are less prevalent in the gut of IBD patients, and there is a reduced concentration of butyrate [205,209]. At the gut level, butyrate has been demonstrated to have anti-inflammatory characteristics, particularly on immune cells and Intestinal Epithelial Cells (IECs) [206,210]. Propionate and butyrate hindered the maturation of DCs, which are crucial for the survival of the adaptive immune system, according to studies conducted on mice As a typical Pattern Recognition Receptor (PRR), TLRs are associated with the development of IBD [157]. TLRs, also known as type I transmembrane receptors, are displayed on a wide range of immune cells [211]. As a result of the adapter protein transmitting the signal, NF-kB and activator protein-1 are activated, which causes inflammatory reactions. The mentioned factors make it likely that TLR signaling and IBD are related: 1) Chronic inflammation may result from TLRs' high sensitivity to activation and extreme hypersensitivity to triggering. 2) It commonly results in an unbalance in the intestinal microbiota and harm to the intestinal mucosa when TLR signaling is inadequate, which eventually causes inflammation [212]. The SCFAs prevent TLRs from over-signaling in the intestines, which reduces inflammation. Consuming more fiber boosts the

amount of SCFAs in the gut and reduces inflammation mediated by TLRs. SCFAs may be effective in treating IBD by targeting TLR4 and TLR2 [213]. Among those who have inflammatory bowel disease, butyrate prevents the release of inflammatory factors mediated by TLR2. The amount of adaptor protein expression is also reduced by butyric acid elevated TLR4 signals decrease the amount of SCFA-producing flora in the gut, which plays a vital role in the development of IBD [214]. Activation of NLRP3 prevents IBD, contrary to earlier studies that suggested NLRP3 activation promotes the disease [215]. SCFAs control the NLRP3 inflammasome, which inhibits IBD. In mice with a healthy gut, it was shown that SCFAs bind to GPR43 and GPR109A to activate the NLRP3 inflammasome [158]. To prevent inflammation, GPR43 promotes NLRP3 inflammasome reduction through a $Ca2+$-dependent pathway, which is activated by SCFAs and necessary for sufficient inflammatory vesicle formation and IL1β release [216]. A shift in the intestinal flora in people with CD and UC makes them more susceptible to inflammation because NOD2 mutations, a crucial part in the control of inflammation, are linked to lower levels of Clostridium group XIVa and IV (bacterial strains that produce SCFAs) and higher levels of Actinobacteria and Proteobacteria [217,218]. NOD2-deficient mice frequently exhibit symptoms of experimental colitis, including weakened epithelial barrier, diminished intraepithelial lymphocytes, decreased synthesis of α-defensin, and poor immunological reactions to harmful microorganisms [86]. Since neutrophils are thought to be the main effector cells in IBD, in human blood-derived neutrophils, acetate, propionate, and butyrate were initially studied [86]. Researchers have studied the effects of SCFAs on neutrophils in the past [219]. A recent study found that propionate also increases neutrophil chemotaxis [121]. The production of superoxide by neutrophils has been shown to be increased by propionic acid. While SCFAs play an important function in neutrophil responses to inflammation mediators like LPS, it remains unclear how they do so. As shown by Tedelind et al. [220], SCFAs significantly reduce TNF production by human neutrophils induced by LPS. Furthermore, the results showed that SCFAs do not inhibit IL-8 production by neutrophils in response to LPS, suggesting that the two pathways by which LPS induces TNF and IL-8 production from neutrophils are distinct [220]. Consequently, GPR43 has been suggested as a plausible mechanism to mediate SCFA's barrier-enhancing and anti-inflammatory effects in IBD, and regulations of GPR43 are currently being investigated as a possible treatment option. By evaluating the effects on human intestinal and immune cells of SCFA and specific GPR43 agonists [221]. The findings demonstrated that SCFA are crucial for improving intestinal barrier performance and reducing immune cell activation. However, it was shown that GPR43 agonists could not take the place of SCFA in the studies carried out [221]. In one study during an eight-week study, eleven patients with distal UC received butyrate enemas or placebo enemas. Antibodies against NF-κB (p65) and CD68 were utilized in double-staining to detect both macrophages and NF-κB [222]. Nuclear translocate d NF-B-positive macrophages were much less after butyrate treatment for 4 and 8 weeks. Butyrate also markedly decreased the quantity of neutrophils in the crypt and surface epithelial along with the lymphocytes and plasma cells in the lamina propria. These findings were significantly linked with a decline in the Disease Activity Index (DAI) [222]. The reduction of NF-κB translocation in lamina propria macrophages is linked to a decrease in DAI and mucosal inflammation in individuals receiving butyrate treatment. Because macrophage-derived proinflammatory cytokines are primarily responsible for maintaining the inflammatory process in UC, butyrate's known anti-inflammatory actions may be largely mediated by a suppression of NF-κB activation in these macrophages (Fig. 2) [222].

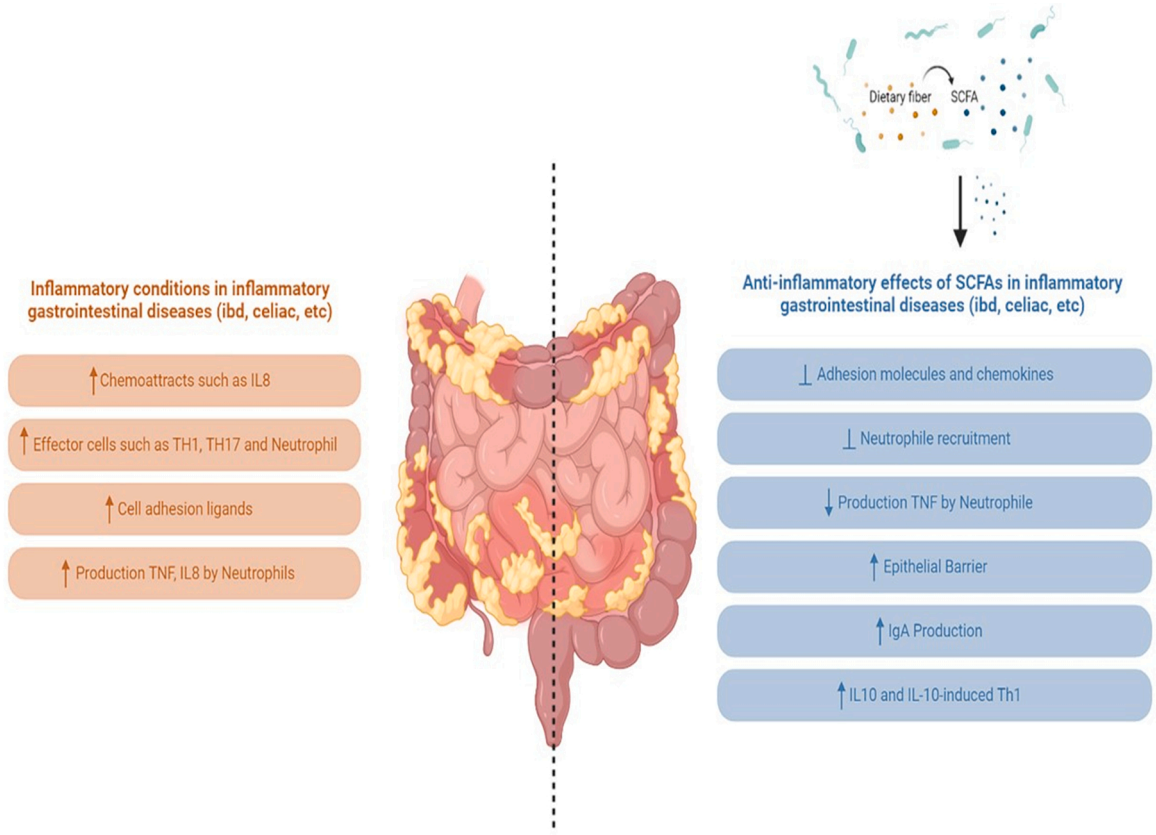

Fig. 2. SCFAs in Inflammatory gastrointestinal diseases. SCFAs have various functions in order to improve the inflammatory conditions of the digestive system in IBD and celiac diseases, the most important of these functions are inhibiting and suppressing adhesive molecules and chemokines, inhibiting the migration and the production of inflammatory cytokines of neutrophils, increased production of anti-inflammatory cytokine IL-10, increased production of IgA and improving the mucosal system of the gastrointestinal tract were noted. SCFAs: Short chain fatty acids, IgA: Immunoglobulin A.

7.3. Celiac

CeD is a chroniautoimmune disease that develops in people with certain genetic predispositions to the gluten protein. Gluten exposure causes adverse reactions in these individuals, such as GI and extra-intestinal symptoms [223]. Researchers have discovered that the bacterial species *Lachnoanaerobaculum umeaense*, *Prevotella*, and *Actinomycetes* display greater diversity in CeD [224]. Genetic factors, the use of antibiotics, and breast-feeding were all linked to the alterations in the microbiota associated with CeD [224]. These elements serve as potential risk factors for dysbiosis. Enteral mucosa cell biology and activities are influenced by metabolites produced by microbes, and signaling pathways controlled by SCFAs are essential for the interaction of gut microorganisms with the host such as propionate, acetate, butyrate, and pentanoate, are produced mainly by colonic bacteria from complex nondigestible polysaccharides such as starch and fiber [224]. Butyrate, which is absorbed from the colonic epithelium, is the preferred fuel for colonocytes. Microorganisms' production of SCFAs allows them to enter the body through the distal colon or portal vein. After there, they move to distant organs where cells absorb, digest, and utilize them in a variety of ways [224]. SCFAs are important modulators of host immunity because they induce antimicrobial peptide production and regulate Tregs. The concentration of SCFAs decreases due to unfavorable gut microbiota status, which is necessary for the host to maintain healthy intestinal function [225]. In fact, they prevent the initiation of inflammatory responses and retain the integrity of the epithelial barrier by controlling the transcription of tight junction proteins, mainly claudin-1. Additionally, the SCFAs promote mucin 2 expressions, control oxidative stress, and immunological reaction, and promote colonocyte proliferation and differentiation to safeguard colonic epithelium [225]. By stimulating TNF-α release, which is caused by IFN-γ production, CeD damages and inflames the intestinal mucosa [226]. Primec et al. [226] claimed that in CeD, acetic and propionic acids may serve as significant disease indicators since they act as potential pro-inflammatory factors. In terms of their ancestry in relation to *Bifidobacterium* and *Lactobacillus*, there is some dispute and more research is needed. There was a significant increase in SCFA levels in the Newly Discovered (ND) group compared to the control group for acetic and propionic acids. There is a possibility that the pathophysiology of CeD has nothing to do with *Enterobacteriaceae* [226]. In contrast to other studies, they found no statistically significant changes in total SCFAs across any patient groups [227,228], who discovered that CeD patients had greater levels of total SCFAs than healthy individuals. It's interesting to see that Lactobacillus species nearly inversely connected with total SCFAs in the ND group and the Control group [229]. According to Tjellström et al. [159] butyrate may have anti-inflammatory properties, whereas acetic acid may have pro-inflammatory effects.

In organoid-derived monolayers produced from CD biopsies, acetate and butyrate exhibit barrier-promoting abilities, and butyrate has been shown to limit gliadin's capacity to stimulate the formation of IL-15 and IFN-γ [230]. Overexpression of IL-15 in the mouse epithelium significantly reduced butyrate-forming bacterial taxa, which increased sensitivity to colonic inflammation [231]. Although changes in SCFAs and bacteria that produce SCFAs have been documented between CD patients and healthy controls [228], additional fundamental investigations are required to validate the protective role, if any, of SCFAs in CD etiology [232]. By promoting TLR ligand-response-induced NF-κB activation in epithelial cells, SCFAs affect the generation of pro-inflammatory cytokines (such as IL-1, IL-6, IL-8, and TNF-α) [161]. A combination of butyrate and propionate inhibits the activation of bone marrow-derived DC (BMDC) by inhibiting the release of IL-6,IL-12p40, and the co-stimulatory molecule CD40 [233]. In a recent study, it was shown that butyrate-exposed DCs produced the immunosuppressive enzymes indoleamine 2,3,-dioxygenase 1 (IDO1) and aldehyde dehydrogenase, which caused forkhead box P3 (FOXP3)+ Tregs to be produced and prevented naive T cells from diffusing into IFN-producing cells (Aldh1A2)[234]. Additionally, propionate-treated mice had DCs that were less able to activate Th2 effector activity and more prone to allergic airway inflammation. These DCs were identified by lower expression of CD40, PD-L2, and CD86 [235]. In several research, it was shown that people with active CeD had lower percentages of beneficial, anti-inflammatory bacteria like *Bifidobacterium* and higher percentages of Gram-negative bacteria like *Bacteroides* and *Eshiershia coli* [227,236]. *Staphylococcus* and *Clostridium* levels are also higher in CeD children, which is the opposite of *Lactobacillus spp.* levels [236,237]. In individuals with CeD, reduced metabolic function (SCFAs) and an altered variety of the microbiota have also been described (Fig. 2) [227,238].

7.4. Multiple sclerosis

MS is an autoimmune disorder that affected the central nervous system (CNS) and is associated with neurological disability and is characterized by inflammation and demyelination of neuronal cells [239]. Usually, young people with 20–30 age are susceptible to this disease and their functional and movement abilities are reduced [240]. Based on a study in 2020, the incidence of MS was reported at 2.1 per 100,000 persons/year which has been increasing around the world since 2013 and often affects women twice as men [241]. Although the exact cause of MS is unknown, environmental, genetic, and lifestyle variables play a role in its development [240]. T and B lymphocytes play a part in inflammation and the demyelination of neuronal cells, which is consistent with the etiology of MS [240].

Recent investigations showed moderate gut dysbiosis in MS patients and reported a probable relation between MS disease and gut microbiome that gut dysbiosis and change in bacterial population can be associated with an inflammatory condition in this disease [242]. Moreover, due to the reported anti-inflammatory and immunomodulatory roles of SCFAs as produced metabolites of gut bacteria, it seems that they can be effective in disorders related to inflammation and the immune system [243]. Based on in vivo studies on MS, and experimental autoimmune encephalomyelitis (EAE), SCFAs cause an improvement of symptoms of disease, and is reported that SCFAs can inhibit inflammation through decreasing inflammatory T cells and enhancing Tregs [243].

Of note, based on some experiments, SCFAs can be a biomarker to consider the recovery process of MS disease [244]. In association with butyrate as an SCFA and MS disorder, it has been reported that butyrate-producing bacteria and serum levels of butyrate in MS patients have decreased (208). Based on a study, butyrate can increase Treg cells number and decrease IFN-γ and IL-17 cytokines in EAE mice under dietary fatty acids [162]. Moreover, administration of oral butyrate to one of the animal models of MS disease causes inhibition of demyelination progress in the disease and by differentiation of oligodendrocyte cells, boosts remyelination which can ameliorate the disease [163]. Animal model studies showed that butyrate-producing bacteria, improve the restoration integrity of the blood-brain barrier (BBB) and consequently reduce the migration of immune cells to CNS through BBB [245].

Studies reported that the amount of propionate in the serum and feces samples of MS patients is decreased. In line with that rate and function of Tregs are diminished in these patients [246]. It was interestingly demonstrated that oral propionate given to MS patients increases the number and activity of Treg cells, which are linked to effective immunomodulatory effects [165]. Also, a positive correlation between propionate level and T follicular regulatory cells (Tfr) number has been reported that fewer levels of serum propionate in MS patients is mediated to a reduction in regulatory activity of the germinal center [247].

The highest amount of SCFAs synthesized by gut bacteria is acetate which is decreased in the serum and feces of MS patients and studies reported this SCFA is negatively related to inflammation [244,247]. Also, a lower amount of acetate with higher-level production of TNF, an inflammatory cytokine, by B cells, has been detected in MS patients

[165]. Regarding SCFA and biomarkers related to MS disease, it has been reported that Nfl, which is a cytoskeleton protein, is one of the most important biomarkers of MS disease and indicates nerve cell damage, there is no correlation between its level and SCFA, which suggests that SCFA are not directly effective on neuronal damage (Fig. 3) [244].

7.5. Systemic lupus erythematosus

One of the most severe chronic and systemic autoimmune diseases, SLE can damage a variety of tissues and organs [248]. The worldwide prevalence of this disease is reported to be 100–50 per 100,000 adults, and its incidence has increased over the past 40 years [249]. Environmental factors (e.g. smoking, and drugs) and genetics can be factors that induce this disease [249]. The overreaction of the immune system, and the development of inflammation, are recognized in the progress of SLE. The heterogeneous clinical manifestations related to this disease have made its diagnosis difficult or delayed [248].

SLE disease is usually characterized by metabolic abnormalities. Intestinal microbiota and SCFA production are factors affecting host metabolism and in line with that, gut dysbiosis in SLE patients is detected [250]. The results indicate that in SLE patients, gut dysbiosis is related to increased lymphocyte activation and Th17 cell differentiation, which maintain the inflammation existing in these patients [251]. According to studies, a decrease in SCFA production in SLE patients is a consequence of *Firmicutes* reduction and *Bacteroidetes* augmentation [252]. A decrease in *Firmicutes*, as a major gut SCFA-forming bacterium, is associated with inflammation, and also, the increase of *Bacteroidetes* leads to the destruction of the integrity of the intestinal epithelium and inflammatory responses in SLE patients [253].

Additionally, investigations showed that following fecal microbiota transplantation (FMT), levels of IL-6 and the CD4 + memory/naïve cells ratio in the peripheral blood of SLE patients were significantly lowered, associated with a large enrichment of SCFAs-forming bacterial taxa and a decrease in inflammation-related bacterial taxa and this study introduced FMT as one of the treatment strategies for SLE patients [166].

Studies show that dietary fiber-derived SCFAs can manage SLE disease by influencing B cell activity and generating antibodies [254]. Resistant starch, which encourages the gut microbiota to digest fiber into SCFAs, has also been shown to reduce the amount of *Lactobacillus Reuteri*, alleviate lupus-like symptoms, downregulate type I IFN pathways, and lower lupus-related mortality [168]. However, unlike the previous studies mentioned above, based on an SLE animal model study, SCFA administration did not result in any alterations to the immune system's phenotype except an increase in Treg frequencies and had minimally positive effects on lupus pathophysiology [169]. Given that inadequate dietary fiber intake has been demonstrated to hasten the development of lupus pathology and related immunological dysregulation, it may be emphasized that SCFAs may play a crucial role by supporting healthy intestinal homeostasis and positive immune effects [169].

7.6. Rheumatoid arthritis

RA disease is a chronic and inflammatory autoimmune disease that is systemic and affects the joints with different degrees of severity [255]. RA commonly manifests as morning stiffness in the impacted joints, exhaustion, fever, and weight loss. Genetics, gender, age, and environmental factors are all potential contributors to this disease's risk factors [255]. Approximately 5 out of 1000 people globally have RA disease. The pathogenesis of RA, which involves chronic inflammation of the synovial membrane, could lead to the destruction of articular cartilage and juxta-articular bone. One characteristic of the RA condition is T and B lymphocytes and monocyte penetration of the synovial membrane in different joints [256].

Although the precise origin of RA disease is still unknown, it is generally recognized that the pathophysiology of the condition is significantly influenced by the gut microbiota. Furthermore, increasing data suggest that gut dysbiosis sets off a chronic inflammatory response that can be connected to the development of the condition [257]. Based on studies, in RA patients, levels of valerate, butyrate, propionate, and acetate were reduced; the first three of these metabolites related positively with the frequency of regulatory B cells (Bregs) in peripheral blood [258]. A study claims that the administration of SCFAs regulates the differentiation of B cells by increasing the frequency of Bregs and reducing follicular B cells which improves the symptoms of this disease [258].

In animal models of arthritis, SCFAs, particularly butyrate, have been demonstrated to be important regulators of the gut joint axis, for instance by reducing osteoclast activities and enhancing bone density. Also, butyrate causes occludin and ZO-1 to form tight junctions, which

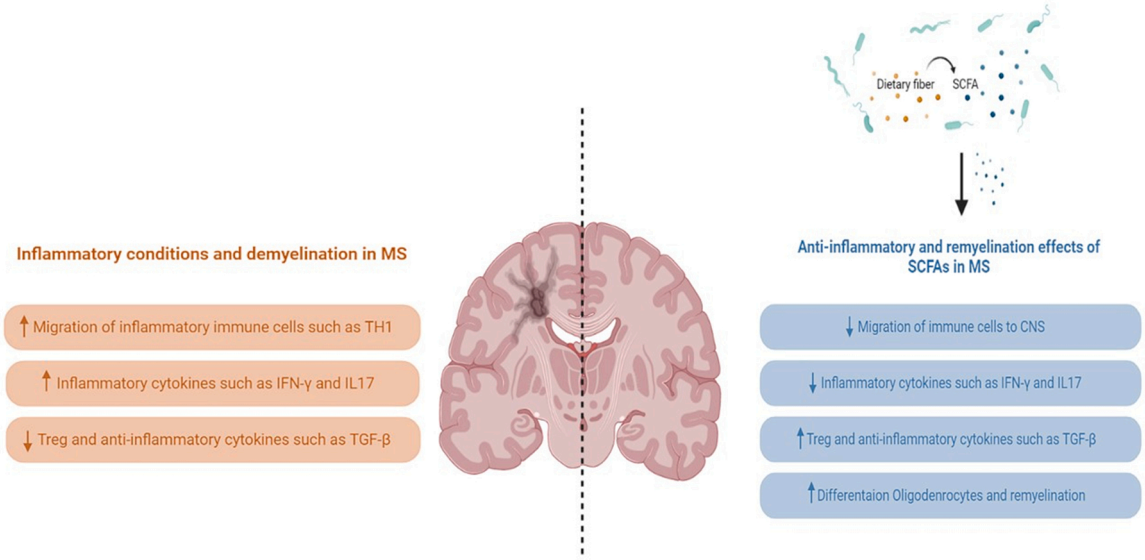

Fig. 3. Function of SCFAs in Multiple Sclerosis. SCFAs have different functions in order to improve the inflammatory conditions of the nervous system in MS, the most important of which is to inhibit the migration of inflammatory cells of the immune system to the CNS, reduce the production of inflammatory cytokines (IFN-γ and IL-17), increase Treg cells and anti-inflammatory cytokines (TGF-β), increased the differentiation of oligondrocytes and remyelination pointed out. SCFAs: short-chain fatty acids, CNS: central nervous system, IFN-γ: Interferon-gamma, TGF-β: Transforming growth factor-beta.

reduces intestinal permeability and the movement of microorganisms and likely inhibits the activation of effector T cells. Furthermore, SCFA promotes the stomach to produce mucus, and B cells to secrete IgA, activate gut Treg cells and suppress NF-kB. As a result, SCFA supplementation, particularly butyrate, may represent a treatment strategy to treat RA [259].

Recent research has demonstrated that SCFAs are crucial in the control of inflammation in RA disease. Mice lacking the SFCA receptors had aggravated RA-related inflammation. In animal models of RA and other inflammatory disorders, butyrate has been demonstrated to reduce inflammation by acting as an endogenous HDAC inhibitor [171]. Also, according to research, SCFA regulates the in vivo metabolism of osteoclasts and bone mass. Paired with a high-fiber diet, SCFA therapy efficiently increases bone mass in rats and protects against postmenopausal and inflammation-induced bone loss. The protective effects of SCFA on bone mass are associated with the inhibition of osteoclast growth and bone resorption in vitro and in vivo, whereas bone synthesis is unaffected [170].

According to the studies, a high-fiber diet in RA patients increases SCFA and thus decreases pro-inflammatory cytokines like IL-18,IL-33, and CCL2, these results show the positive and improving effects of SCFAs in the improvement of RA disease [172]. Additionally, in vitro studies show that exposing synovial fibroblasts to propionate or a normal combination of SCFAs impeded cell migration, prevented the synthesis of inflammatory mediators, and slowed immune-regulatory fibroblasts from proliferating (Fig. 4) [260].

7.7. Sjögren's syndrome

It has been found that the SCFAs produced by commensal species taxa's fermentation of alimentary carbohydrates, in particular butyrate (and to a smaller amount extent propionic and acetic acid), have potent immunomodulatory effects. SCFAs[174,261]. Epithelial cells use SCFAs as a source of energy, which also stimulates gut motility through serotonin, speeds up colon transit, and simultaneously directly controls sympathetic nervous system activity via the GPR41 at the sympathetic ganglion level [262].

There is data that the gut microbiota plays a function in regulating immune responses between Treg and Th17 cells and in triggering autoimmune diseases like Sjögren's syndrome [263]. By decreasing nuclear factor-κB and inhibiting HDAC, butyrate increases H3 acetylation on the Foxp3 locus in Treg, thereby enhancing transcription factor stability and activity. HDAC maintains chromatin in a compact state to stop gene transcription. Further, butyrate can activate mTOR and Blimp-1 factors in CD4 +T cells [262,264]. Some SCFAs increase the apoptosis of effector T cells and enhance the expansion of Tregs in the gut, thus helping to devastate infection and cause autoimmune illness [265]. Another recent study found that SCFA butyrate might influence B cell development and enhance B10 cell activity in part through an AhR-dependent transcriptional pathway. These are Bregs that maintain immune homeostasis by producing IL-10 [266].

Recent evidence has linked Sjogren's syndrome with dysbiosis of the gut flora, which is provided as a possible therapeutic target [174]. There are, however, very few studies on gut dysbiosis in Sjogren's syndrome [263]. Continuous research using metagenomics has shown how gut bacteria cause distant autoimmunity. Additionally, recent research raises the possibility that the gut microbiome and autoimmune dry eye are related [267]. It has been shown that SCFAs generated in the gut have been shown to have anti-inflammatory properties that may broaden away from the digestive system to other parts of the body, including the eyes. On the other hand, the reduction of microbiota species that generate anti-inflammatory mixtures such as butyrate in patients with

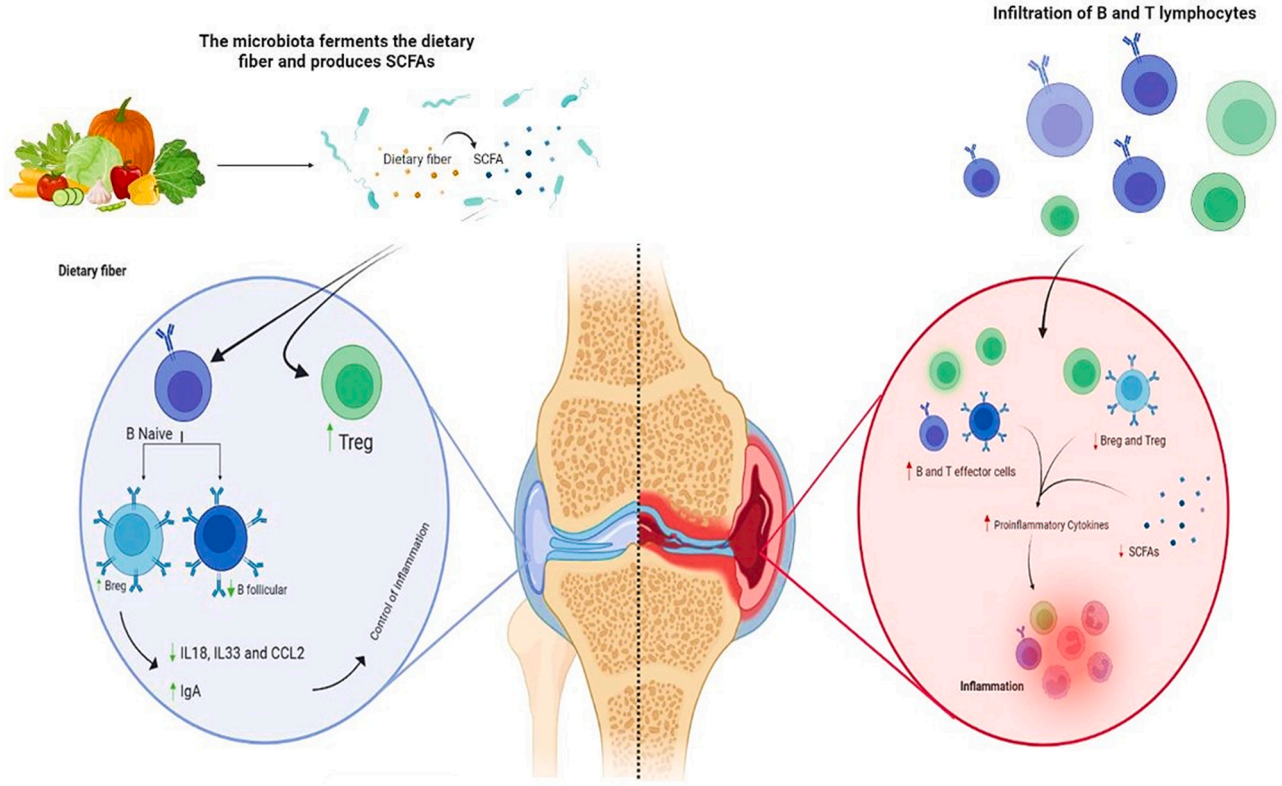

Fig. 4. Role of SCFAs in rheumatoid arthritis. As indicated in the figure, SCFAs have different functions in order to improve the inflammatory conditions in the joints of rheumatological diseases, especially RA, the most important of which are the reduction of follicular B cells, the increase of Treg and Breg cells, the increase of IgA production and the decrease in the production and secretion of cytokines. and inflammatory chemokines such as IL-18, IL-33 and CCL2. SCFAs: Short chain fatty acids, RA: Rheumatoid arthritis, IgA: Immunoglobulin A.

Sjogren's syndrome can lead to worse dry eye pathology [268].

Gut microbiota imbalance can lead to Th1 and Th17 cell imbalance, Treg polarization, increased intestinal epithelial permeability, and SCFA production. In addition to adjusting probiotic therapy for each condition, it may be helpful to inquire about the dysbiotic types of the gut flora in any autoimmune illness [262,263]. It has been demonstrated that some Clostridia clusters can induce Tregs and create SCFAs to aid in the formation of Tregs. Similar to this, Bacteroides species may produce polysaccharide A, which blocks the Th17 inflammatory responses and elevate mucosal tolerance in addition to colonization. Given our results, depletion of commensal organisms such as *Clostridium* and *Bacteroidetes* may affect the proportion of Th17 to Treg cells, pushing the body towards autoimmunity [265,269].

Except for an increase in *Streptococcus* and a decrease in *Leptotrichia* and *Fusobacterium*, there is no substantial change in intestinal microbial composition between Sjogren's patients and healthy people [270]. In the study by Jayoon Moon et al. [263], *Eubacterium halli* was reduced in Sjögren's disease patients compared with controls. Another butyrate-producing bacterial species, on the other hand, showed no significant changes. This research suggests a link between Sjogren's syndrome and intestinal barrier failure caused by butyrate [263]. A decrease in complement components and greater amounts of fecal calprotectin are reported in Sjogren's patients with severe dysbiosis (decreased *Alistipes* and *Bifidobacterium*), a severe form of the disease [270].

7.8. Graves' disease

Thyroid autoimmune disease, as represented by Graves' disease, is the most frequent organ-specific autoimmune condition. Several potential pathways are postulated to contribute to changed microbiota composition in the gut and decreased bacterial products, including modulating the entirety of intercellular junctions and microbial transcriptomic, proteomic, and metabolic alterations [271]. The first theory explaining how intestinal bacteria affect thyroid function originally emerged in the early 1900 s. According to Sir Arbuthnot Lane, persistent constipation may cause systemic dysfunction, including "exophthalmic goiter" (also known as Graves disease), because of the intestines' ability to absorb toxins. Based on this hypothesis, D. J. Harries concluded that parenchymatous goiter results from an excessive amount of tryptophan being destroyed, but Graves disease is caused by an imbalance of gut flora [272]. The intestinal microbiota species in a healthy gut should be able to keep a balance between Treg and Th17. The gut microbiota could be upset by various environmental factors, which can tilt the scales in favor of autoimmune and inflammatory reactions [273]. Dysbiosis of the gut flora is thought to underlie two pathways leading to Graves' disease. (A) Antigenic mimicry: because they closely resemble autoantigens in structure or sequence, antigenic mimics in the gut microbiota may induce plasma cells to generate antibodies that bind thyroid-stimulating hormone receptors on thyroid follicular cells and orbital fibroblasts [274]. The effect of thyroid hormones on gut health depends on how they interact with enterocytes directly. In these cells, T3 modulates the differentiation and function of the cells by inducing intestinal alkaline phosphatase (IAP) and suppressing lactase gene transcription. T3 may be accompanied by SCFAs generated by the microbiota present in the gut lumen during these activities [269]. Together with thyroid hormones, SCFAs can build intercellular tight junctions [275]. (B) Balance issue between Th17 and Treg cells: SCFA, which can boost the generation of Tregs, are one example of a beneficial anti-inflammatory metabolite that may be reduced or absent due to intestinal dysbiosis [274]. Fragmented filamentous bacteria can encourage Th17 cell expansion and differentiation. Graves disease progression may be accelerated indirectly by the imbalance between Th17 and Tregs [274].

The maturation of immature T lymphocytes found in the lymphoid tissue associated with the stomach is a process that is influenced by gut microbiota. The balance between pro-inflammatory Th17 (present in many autoimmune diseases) and anti-inflammatory Treg (up to 50% of circulating lymphocytes at any given moment dwell in the gut-associated lymphoid tissue) is influenced by species in the gut. For instance, Treg is favored by SCFAs, such as butyrate [273]. In 2014 study by Zhou et al. [276] highlighted the significance of gut dysbiosis as a cause of Graves' disease due to a significant decrease in *Lactobacillus* and an increase in *Clostridium* and *Enterococcus* [276]. Compared with healthy people, research figure out that patients with Graves' disease had reduced variety in their gut microbiota. *Prevotellaceae* and *Pasteurellaceae* were discovered in much larger concentrations in Graves' disease patients than in healthy controls, but *Enterobacteriaceae*, *Veillonellaceae*, and *Rickenellaceae* were found in significantly lower concentrations. Additionally, antibodies against *Helicobacter pylori* and *Yersinia enterocolitica* were found; however, not all individuals with Graves' disease showed these responses [277]. Investigation into the link between Graves' disease and intestinal microbiota is scarce. However, in people with Graves' disease, thyroid hormone levels are correlated with the intestinal microbiome and the diversity of intestinal bacteria [278].

Seasonal variations in the nasal microbiota and a decline in diversity throughout the first year of life are seen. Additionally, the relapse rate for Graves' illness tends to increase in the spring and summer. To uncover potential connections between the microbiome and disease development, more research is required [262]. Also, the function of SCFAs in Graves' disease is poorly understood. In 2020, Su et al. [278] found that propionate had an impact on Graves' illness. Several research in the scientific literature reporting differences in the intestinal microbiota, including SCFA levels in the compromised thyroid status, which tend to support a link between SCFA and thyroid function [278]. A novel method for treating and managing the associated illnesses has been made possible by the recently discovered function of gut dysbiosis in Graves' disease, but regrettably, there is no reliable evidence and consistent research for it [276].

7.9. Hashimoto's thyroiditis

The role of gut flora in the pathogenesis of Hashimoto's thyroiditis has been suspected since the late 1980 s. This study showed that rats retained under pathogen-free circumstances were higher resistant to the progress of autoimmune thyroiditis than rats retained commonly [279]. Given their shared embryological origin, the thyroid and gut explain certain physical and physiological parallels between their follicular cells [280]. Since some bacteria are diminished in Hashimoto's thyroiditis and Graves' disease, there has been proposed that the composition of the gut and mineral adjustment may have an impact on both conditions [275].

Apoptosis and inflammation in the thyroid tissue are triggered by the expansion of Th1 and Th17 lymphocytes in the thyroid gland, respectively. The gut microbiota promotes further differentiation of Th17 lymphocytes and controls the interaction between regulatory (Treg) and effector (Th17) cells [281]. Although the exact mechanisms have not yet been described, it is believed that the presence of SCFAs may be associated with several various aspects of thyroid operation [282]. Epidemiological and experimental studies have therefore shown that increased fiber consumption reduces the risk of metabolic diseases. This function has been found to occur by altering the composition and diversity of the gut microbiota and increasing SCFAs production [283].

The following potential microbial-related pathways are the essential ways that the gut microbiome affects the thyroid [280]. First, dysbiosis causes the intestinal barrier to become disrupted and intestinal permeability to rise, allowing antigens to enter the bloodstream and trigger the immune system. Second, the antibodies in the bloodstream may interact with the bacterial antigens and increase the thyroid gland's inflammasome activity [280]. Third, SCFAs, metabolites of fiber-fermenting commensal bacteria, are thought to be essential for the growth, function, and regulation of the immune system [280]. For instance, butyrate,

an SCFA, is linked to lower levels of TNF-a and IL-6 as well as inhibited NLRP3 inflammasome activation via GPR109A [280].

Studies have shown that SCFAs concentrations may be indirectly impacted by thyroid dysfunction, but the thyroid has also been shown to be sensitive to diversity in the gut microbiota [282]. The findings imply that thyroid dysfunction has an indirect effect on the amount of SCFAs in the stool [284]. The basic gut microbiota component *Lachnospiraceae* colonized in the host's digestive system from birth [278]. Additionally, members of the *Lachnospiraceae* family are the primary microbiota generating SCFAs, controlling the activation of inflammasomes [280]. Additionally, certain bacteria may make the body more permeable by triggering the inflammatory system, which would allow poisons, antigens, or SCFAs to enter the bloodstream [280]. *Bacteroidetes*, *Bifidobacterium*, *Enterobacteria*, and *Faecalibacterium*, abundant energy sources for the host, create the majority of SCFAs, which are principally butyrate, acetate, and propionate [280]. One of the major significant metabolites generated by butyrate-forming bacteria, such as *Firmicutes*, is butyrate, which improves mucosal immunity and the intestinal barrier [280]. Intestinal permeability may thus have risen in the autoimmune thyroid disease group due to the reduced phylum *Firmicutes* [280].

In addition to supplying enterocytes with energy, SCFAs, which are by-products of anaerobic microbial fermentation, may promote enterocyte differentiation and increase the integrity of the epithelial barrier when combined with thyroid hormones, particularly T3 [285]. Changes in microbiota composition enhance the outbreak of Hashimoto's thyroiditis [178]. Microbes affect the level of thyroid hormones by regulating the absorption and breakdown of iodine and the liver-intestinal cycle [178].

8. SCFAs as a therapeutic target in autoimmune diseases

It has long been understood that the gut microbiota affects the effectiveness and side effects of therapy [286]. Therapy can cause intestinal microbial dysbiosis, which in turn causes intestinal mucositis as a result of several effects, including inflammation and oxidative stress, decreased gastrointestinal permeability, changes in the way mucus is formed, impaired epithelial repair, and immune factor secretion [287]. The presence of SCFA-producing bacteria facilitated intestinal homeostasis and mucosal healing. In chemotherapy-induced colitis, direct application of SCFAs like butyrate has been shown to increase IL-10 and decrease IL-12 and TNF-a. However, recent research by He et al. [288] showed that butyrate and oxaliplatin together promoted antitumor immunity. It improved tumor control in mice bearing MC38 colorectal cancer tumors by favoring cytotoxic T lymphocyte (CTL) effector function. Notably, butyrate supplementation in vivo improved the therapeutic activity of anti-programmed cell death 1 (PD-1) immune checkpoint blocker therapy in this situation [288]. This outcome is consistent with a recent clinical study that demonstrated the effectiveness of SCFAs and PD-1 immune checkpoint blockers in the treatment of solid cancers [289].

The protection against release and absorption in the small intestine provided by esterification of SCFAs to resistant starch. As compared to unmodified resistant starch, this chemical modification produces effective and preferential transport of each SCFA to the colon by combining both postbiotic and dietary methods [290]. Consuming these carbohydrates therefore causes a substantial rise in SCFA levels in both healthy individuals' feces and the stoma digesta of patients with ileostomies [291]. Additionally, eating 40 g of butyrylated starch every day prevented healthy controls from developing colonic tumourigenic adducts, which were brought on by eating 300 g of high-red meat food every day [292]. These starches provide NOD mice with notable defense against autoimmune T1D [293]. As a more effective method than using starch, esterification of propionate to inulin has also been reported [294]. It is estimated that 10 g of propionated inulin can deliver the same amount of propionate to the colon as 90 g of non-starch polysaccharide. Additionally, it has been noted that this dose increases post-prandial plasma PYY and GLP-1, and that long-term ingestion inhibits weight gain in obese people. These studies highlight the therapeutic benefits of targeted and effective SCFA delivery to the colon, highlighting a potentially appealing strategy for use in upcoming randomised control trials.

Several fiber-utilizing bacteria that are potent SCFA makers dominate the human microbiota [295]. According to recent studies, microbial metabolites SCFAs co-evolved with the host as active signaling molecules with a variety of advantageous functions for the host as well as potential therapeutic potential. For instance, mice lacking the molecule were more likely to develop intestinal inflammation and colitis-associated cancer than wild-type (WT) animals, indicating that the surface receptor GPR109A is crucial for butyrate-mediated protective effect in the gut [296]. It should be noted that systemic activity of these microbial metabolites may also contribute to the beneficial effects of SCFAs on human health. It has been demonstrated that giving mice a high-fiber diet will boost their blood levels of SCFAs and reduce lung inflammation brought on by allergic reactions[297]. In addition, SCFAs reduced the severity of the condition in the experimental murine rheumatoid arthritis model [298]. These studies demonstrate how inexpensive and non-pharmaceutical methods, such as medical food created to meet particular needs, may prevent or treat autoimmune diseases in humans. Propionate has been demonstrated to slow the progression of experimental EAE in mice by having a long-lasting effect on Tregs derived from the lamina propria [299].

A pioneering research has shown that in GF mice mono-colonized with an SFB, the SCFA valerate totally reverses Th17-mediated EAE development [300]. SFB is a commensal bacteria that has been linked to the development of EAE in mice and the induction of Th17 responses in the gut. [301]. Interestingly, the ability of SCFAs to affect the physiology of the host is connected with more than only positive outcomes. Excessive SCFAs have been shown to encourage T cell-mediated renal tissue inflammation in an experimental model of renal illness, along with progressive ureteritis and hydronephrosis [302]. Induction of icteric hepatocellular carcinoma (HCC) in mice has been linked to intake of dietary soluble fiber and the generation of SCFA butyrate [303]. To reduce potential negative side effects and allow the SCFA therapy of inflammatory and autoimmune illnesses in humans, a greater knowledge of the functional interaction between microbial metabolites and host metabolism is required.

9. Conclusion

The human gut microbiota is an environmental factor that controls the host immune system and upholds tolerance. Accordingly, dysbiosis in the gut microbiota was linked to a variety of illnesses, such as cancer, immunological disorders, neurological conditions, and other diseases. Bacteria produce metabolites in part to control the immune responses of the host. The immune responses of host receptors and target molecules are substantially altered by a variety of bacterial metabolites, including SCFAs, according to mounting data. The intestinal mucosa's structural integrity is greatly influenced by the SCFAs that our gut bacteria produce, including butyrate, propionate, and acetate. Different signals are produced by SCFAs and their receptors in response to modifications in immunological, dietary,

A significant finding of our study was that SCFA injections reduced the severity of lymphocyte-mediated systemic autoimmune inflammatory disorders including EAE and Collagen-induced arthritis (CIA) by reducing Th1 and increasing Tregs. Conversely, SCFAs supported the expansion of antibody-induced inflammation. The prevention of systemic inflammatory illnesses will come about as a result of a fuller understanding of the impacts of microbial metabolites. The gut microbiota has attracted a lot of attention recently, propelling it to the forefront of academic research. According to recent studies, dysbiosis in gut bacteria may have a role in the emergence of several diseases. The biochemical messengers generated by the microbiota are a crucial part of this crosstalk. The bidirectional relationship between the microbiota and its

host could be mediated in some ways. SCFAs produced by the gut microbiota are thought to play a function in immune and GI physiology.

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Declaration of Competing Interest

Nothing.

Data Availability

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