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Review

Immunomodulatory Properties of Probiotics and Their Derived Bioactive Compounds

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Abstract: Immune system modulation is an intriguing part of scientific research. It is well established that the immune system plays a crucial role in orchestrating cellular and molecular key mediators, thus establishing a powerful defense barrier against infectious pathogens. Gut microbiota represent a complex community of approximately a hundred trillion microorganisms that live in the mammalian gastrointestinal (GI) tract, contributing to the maintenance of gut homeostasis via regulation of the innate and adaptive immune responses. However, impairment in the crosstalk between intestinal immunity and gut microbiota may reflect on detrimental health issues. In this context, many studies have indicated that probiotics and their bioactive compounds, such as bacteriocins and short chain fatty acids (SCFAs), display distinct immunomodulatory properties through which they suppress inflammation and enhance the restoration of microbial diversity in pathological states. This review highlights the fundamental features of probiotics, bacteriocins, and SCFAs, which make them ideal therapeutic agents for the amelioration of inflammatory and autoimmune diseases. It also describes their underlying mechanisms on gut microbiota modulation and emphasizes how they influence the function of immune cells involved in regulating gut homeostasis. Finally, it discusses the future perspectives and challenges of their administration to individuals.

Keywords: probiotics; bioactive compounds; bacteriocins; SCFAs; immunity; immunomodulatory properties; gut microbiota

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1. Introduction

The intestine provides a fruitful environment for the establishment of balanced relationships between commensal bacteria and immune cells [1]. The evolution of this diverse ecosystem over time has occurred through consecutive exposures to multiple antigens. The cellular and molecular components comprising the gut immunity are constantly under intimate interaction with intestinal commensal microbes, thus contributing to the modulation of immune responses as well as the maintenance of gut homeostasis [2]. Alterations in gut microbiota composition may lead to gut dysbiosis, thereby activating various signaling cascades that are implicated in the maturation, differentiation, and proliferation of gut immune cells. Disturbance of this complex microbial community has been directly associated with the development of severe health issues [3], including metabolic disorders [4], chronic inflammation [5], cancer [6], cardiovascular diseases through the gut–heart axis [7], and neurodegenerative diseases through the gut–brain axis [8]. In this context, probiotics have been suggested as a promising treatment strategy for the restoration of the intestinal microbial diversity [9].

Probiotics are microorganisms that confer health benefits to the host when administered in adequate amounts [10]. Bacterial strains with accredited probiotic properties, which include tolerance to intestinal conditions, ability of adherence to epithelial cells, and cell-surface hydrophobicity [11], were found to counteract infections through modulation of gut immunity [12]. Probiotics exert their immunomodulatory properties on the host in several ways, including colonization of the perturbed mucosal barrier, competitive exclusion

and inhibition of harmful invading pathogens, production of bioactive compounds [13], enhancement of anti-inflammatory cytokine production [14], detoxification of virulent substances [15], and recruitment of various immune cells [16].

Bioactive probiotic molecules include amino acids, vitamins, exopolysaccharides, enzymes, short chain fatty acids (SCFAs), and bacteriocins [16,17]. SCFAs are metabolic by-products of non-digestible fiber fermentation [18], while bacteriocins comprise a heterogeneous group of peptides with antimicrobial activity against pathogens [13]. The profound effect of SCFAs, tryptophan catabolic products, and secondary bile acids originating from bacterial metabolism on the immune system–gut microbiota crosstalk has recently been reviewed [1,3]. Although studies on bacteriocins mainly focus on particular commercially available forms and their effects on host health [19], their contribution in the modulation of the immune system has also been reported [20,21]. Therefore, the utilization of bioactive compounds for therapeutic purposes comprises a new field of research investigations.

This review focuses on the underlying mechanisms that configure the intricate interaction between probiotics, bacteriocins, and SCFAs with the host immune cells. Understanding the impact of probiotics and probiotic derived compounds on gut immunity is challenging as well as extremely significant in order to develop efficient therapeutic strategies for the amelioration of life-threatening diseases.

2. Hallmarks of Innate and Adaptive Immunity

The first step in host immunoprotection from invading pathogens is their identification, conducted by the pattern recognition receptors (PRRs) [22], which, based on their localization, are classified into transmembrane receptors (toll-like receptors, TLRs), and intracellular receptors (NOD-like receptors, NLRs) [23]. Their action is related to the recognition of miscellaneous signaling molecules, including microbe-associated molecular patterns (MAMPs) on pathogens and endogenous damage-associated molecular patterns (DAMPs) on host cells [24,25]. PRRs bridge innate (nonspecific) and adaptive (specific) immunity [26], with both immunity types functioning as reciprocal defense mechanisms to provide protection against inflammatory or autoimmune diseases [27].

The innate immunity mainly involves anatomical and physical barriers such as skin and mucous membranes, the microbiota, chemical barriers such as antimicrobial molecules and enzymes, and specialized effector cells promoting phagocytosis of foreign pathogens, rendering it the first line of defense [27,28]. Innate immune response distinguishes normal host cells from intruding pathogens via the identification of pathogen-associated molecular patterns (PAMPs) and of endogenous molecules released from damaged cells (DAMPs), a process mediated by PRRs [27]. The interaction of PAMPs with PRRs elicits an intracellular signal transduction in immune cells [29]. A great variety of components, including antimicrobial enzymes (e.g., lysozyme), acute phase proteins in blood serum (e.g., complement factors, C-reactive protein), antimicrobial peptides (AMPs) (e.g., defensins), cells with phagocytic capacity (i.e., neutrophils, monocytes, macrophages, and dendritic cells (DCs)), and pro-inflammatory cytokine producing cells (e.g., macrophages, mast cells, natural-killer (NK) cells) act in synergy in addition to physical barriers [14,27]. If pathogens manage to penetrate the first line of defense, the adaptive immunity is activated [28].

Adaptive immunity, as a second line of defense against pathogens, is related to antigen-specific responses and provides long-lasting immunological memory to the host [28]. Unlike the immediate action of innate immunity from minutes to hours, the maximum response of adaptive immunity is observed days after exposure to an antigen [14]. The connection between innate and adaptive immunity depends on the activation of professional antigen-presenting cells (APCs), which include DCs, macrophages, and B cells [28,30]. The two main classes of adaptive immunity, humoral and cell-mediated immune response, are mediated by B cells and T cells, respectively [31]. B cells, following maturation, migrate through blood to lymph nodes, where they are bound to foreign antigens, proliferate, and further differentiate into antibody-secreting plasma cells and memory B cells [28,32]. Plasma cells secrete five distinct types of immunoglobulins (Ig) to directly neutralize

antigens or indirectly mark the pathogens for destruction. Memory B cells present extended survival and immediately respond upon re-exposure to the same antigen [32,33]. T cells, the mediators of cell-mediated immunity, mature in thymus to naïve T cells [33], which interact with the major histocompatibility complex (MHC) expressed on the surface of APCs [32]. Following this interaction, they proliferate and differentiate into CD4+ T helper cells (Th cells) and CD8+ cytotoxic T cells. Although CD8+ T cells are critical for the host defense against virally infected cells and tumor cells, those that carry out the action of stimulating other immune cell types are CD4+ T cells [28,32]. The latter can differentiate into seven major subtypes [34], namely Th1 [35], Th2 [35,36], Th9 [37], Th17 [38], Th22 [39], T regulatory (Treg) cells [36,40], and T follicular helper (Tfh) cells [41], and are distinguished by the expression of specific cytokines and transcription factors [33]. The uncontrolled Th cell-mediated immune responses have been linked to the appearance of autoimmune disorders and other diseases. The balanced regulation of particular T cell subtypes comprises an important key element in the maintenance of a strengthened immune system [34,38].

3. Gut Microbiota and Immunity Crosstalk in Health and Disease

The gut microbiota represents a group of microorganisms that are strictly compartmentalized to the intestinal lumen of the mammalian gastrointestinal (GI) tract [42]. This complex microbial community that harbors the gut involves more than 1000 bacterial species [43] which contribute to the maintenance of host health. A balanced gut microbiota combats harmful opportunistic pathogens while showing tolerance to beneficial commensal bacteria, and thus it is directly associated with the establishment of gut homeostasis [44]. Gut microbiota has a prominent participation in the execution of various gut functions, such as degradation of unmetabolized dietary components, production of essential nutrients, and secretion of bioactive compounds with anti-inflammatory and immunomodulatory properties, such as SCFAs and bacteriocins [3,45]. Gut microbiota imbalance, known as gut dysbiosis, is often implicated in the development of acute or chronic inflammation and oxidative stress, provoking grievous health disorders [24]. Changes in the composition and diversity of the gut microbiota are associated with increased susceptibility to non-communicable gastrointestinal diseases [42], such as inflammatory bowel disease (IBD) or colorectal cancer (CRC), metabolic disorders including obesity or type 2 diabetes [46], and cardiovascular and neurodegenerative diseases [47].

Although the connection between diseases and disrupted gut microbiota composition has been documented [47,48], it is still ambiguous whether gut dysbiosis is the cause or consequence for the development of detrimental health issues [49]. It is generally argued that resilience, defined as the ability of an ecosystem to return to its original state after perturbation caused by drug administration, invasion of pathogens, and unhealthy lifestyle habits, constitutes the preponderant factor for a healthy gut microbiota [50]. Resilient microbiota is often associated with increased complexity and diversity of gut microbial communities [51]. However, the determination of a healthy gut microbiota, which might contribute to personalized medicine approaches, has not been achieved yet. This lack of evidence is due to the microbiome diversity among individuals and age groups, as demonstrated by the Human Microbiome Project, rendering the need for further research imperative [52].

Considering the fact that approximately 70% of immune cells reside in the gut [51], the interaction of gut microbiota with the intestinal immune system is a prerequisite towards the achievement of a balance between inflammation and immune tolerance [48]. The intestinal immune system comprises four main compartments: the gut-associated lymphoid tissue (GALT), the mesenteric lymph nodes (MLN), the lamina propria (LP), and the epithelial tissue [53]. GALT utilizes multiple mechanisms in order to eliminate the presence of pathogens in the intestinal lumen of mammals [54] and consists mostly of aggregated lymphoid follicles, the Peyer's patches, which are characterized as the immune sensors of the intestine [55]. Peyer's patches contribute to the generation of IgA-producing

B cells [2] and are covered by the follicle-associated epithelium (FAE), the interface between the intestinal lumen and the GALT [55]. Except for the intestinal epithelial cells (IECs), two distinct types of specialized epithelial cells are incorporated in the FAE: microfold (M) cells, which recognize various mucosal antigens and transfer them to the LP, where the underlying APCs stimulate the adaptive immune response [54,55], and goblet cells, which are involved in the secretion of mucus [3]. The FAE serves as an effective barrier which enhances the isolation of host immune cells residing in the LP from commensal or pathogenic bacteria [3] and may be disrupted in case of gut dysbiosis [51].

Several studies in germ-free (GF) mice, a representative model system of immunodeficiency, have indicated the supreme impact of gut microbiota on the development of the immune system [44,48]. In comparison to GF mice, which are known to exhibit low concentrations of secretory IgA [3], wild-type mice administered intragastrically with commensal bacteria were found to produce great amounts [56]. Additionally, GF mice have poorly developed GALT, including fewer and smaller Peyer's patches and MLNs, while their mucosal barrier is thinner compared to wild-type animals [3,57]. In this context, the necessity of intestinal commensal bacteria in defining the differentiation of immune cellular components has been demonstrated [58,59]. Impairment in immune system–gut microbiota crosstalk may result in serious repercussions, such as deviant immune responses, systemic distribution of commensal microbes, and vulnerability to pathogenic infiltration [60].

4. Immunomodulatory Properties of Probiotics

Probiotics are non-pathogenic distinct microorganisms, which provide health benefits when administered in adequate amounts to the host [10], contributing to the maintenance of gut microbiota homeostasis [61]. They are considered to be one of the most valuable options regarding the restoration of microbial diversity [61] and the treatment of infections caused by antibiotic resistant bacteria or invading viruses [24,54]. However, the precise molecular mechanisms via which they confer their positive effects have not been completely elucidated [9].

The effects of probiotic bacteria on immunity are exerted through epithelial colonization with simultaneous induction of mucin secretion [61], production of several bioactive compounds [24], competitive exclusion of pathogens by preventing their adherence on the intestinal epithelial surface [54], and inhibition of pathogens' proliferation through competition for essential nutrients [2,61,62]. The immunomodulatory properties of probiotics vary between individuals and are mostly attributed to the release of cytokines and chemokines from immune cells [14], the activation of TLRs [2,63], or the inhibition of the nuclear factor-κB (NF-κB) pathway [64,65]. Probiotics are also involved in the regulation of the JAK/STAT and the mitogen-activated protein kinase (MAPK) signaling pathways via the secretion of cytokines and AMPs, thus promoting the mucosal and systemic immune response [64,66]. It is well established that cellular fragments or surface molecules of probiotics can trigger the phagocytic capacity of macrophages and DCs [67–69] while contributing to the enhancement of NK cells [70,71] and CD8+ T cells' cytotoxic activity [72]. The significance of probiotics in inducing the maturation and differentiation of adaptive immune cells through modulation of innate immune cells has been designated [73,74]. Upon adherence to the IECs, probiotics induce the secretion of cytokines leading to the activation of Tregs, the key mediators in maintaining gut homeostasis [2,51,75]. The increased production of the anti-inflammatory cytokine interleukin (IL)-10 by Tregs to the detriment of pro-inflammatory cytokines in the colonic mucosa may suppress inflammatory responses [51] and stimulate immune tolerance to commensal microbes [2,75]. In regard to the required balance of T cell subtypes for the proper function of gut immunity [44], probiotics promote a shift from Th2 to Th1 cells, in order to restrict allergic reactions and control autoimmune disorders [51,54]. Furthermore, the association of probiotics with IECs triggers the maturation of DCs and the subsequent induction of Tregs, thus promoting the immunoglobulin class switching by mature B cells, in the Peyer's patches, towards the secretory IgA [76]. The secretory IgA plays a significant role in preventing the interaction

of pathogens with epithelial receptors, preserving the integrity of the mucosal barrier, and neutralizing bacterial toxins on the mucous membrane [77,78].

5. Probiotic Derived Bioactive Compounds and Immunity

Probiotics produce a great variety of substances, which exhibit growth-inhibitory action against several pathogens and present a distinct effect on the microenvironment abiotic factors [79]. The metabolic products secreted by probiotic bacteria, also known as postbiotics, include vitamins, organic acids, SCFAs, neurotransmitters, flavonoids, amino acids, enzymes, bacteriocins, exopolysaccharides, cell wall fragments, teichoic acids, and biosurfactants [24,80]. A concise summary has recently highlighted some general features of postbiotics in immune response stimulation [24], and the immunomodulatory properties of exopolysaccharides and cell-envelope components [81,82], bacterial lysates, and cell-free supernatants [83,84] have been extensively reviewed. This review emphasizes the current knowledge regarding the effect of bacteriocins and SCFAs on immune cells.

5.1. Bacteriocins

5.1.1. General Features of Bacteriocins

Bacteriocins comprise a miscellaneous group of bacterial peptides, which display antimicrobial activity against other bacteria. Their inhibitory activity can range from narrow to wide, whether they eliminate only bacterial strains that are closely related to the producer bacterium or non-related species [85]. Both Gram-positive and Gram-negative bacteria can secrete bacteriocins [86,87]. To protect themselves from being killed by their own bacteriocins, most of bacterial strains have developed self-defense mechanisms, such as the production of self-immunity proteins and the utilization of efflux pumps [13].

Bacteriocins are small proteinaceous molecules, mostly ribosomally synthesized, with extraordinary and diverse characteristics in terms of molecular weight, net charge, pH, and heat tolerance, as well as physicochemical properties [88]. The secretion of bacteriocins can be modified by several abiotic factors, as well as the producer bacterial strain [89], and takes place mainly in the late exponential growth phase and the early stationary phase [88]. Bacteriocins are considered to be potential candidates for therapeutic use, due to their effectiveness against multidrug resistant bacteria (MDR) [87], since they form pores on the cell membrane of the target cell, a process that contributes to the induction of cell death and prevention of drug resistance development [90]. Bacteriocins bind directly on the cell membrane presumably in the absence of a specific receptor [91].

The predominant producers of bacteriocins are lactic acid bacteria (LAB), a distinct group of Gram-positive bacteria with particular interest due to their "generally recognized as safe" (GRAS) status [79,92]. LAB strains produce lactic acid as a main product of carbohydrate fermentation and include various genera, such as *Pediococcus*, *Leuconostoc*, *Lactococcus*, *Enterococcus*, *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* [21,88]. They share common metabolic characteristics, including the ability of bacteriocins and SCFAs production [92,93]. LAB bacteriocins present great variety, specificity, potential in co-administration with other drugs [87,94], and stability in a wide range of physicochemical conditions. The lack of toxicity of bacteriocins and the absence of bacterial resistance to them has been attributed to their short biological half-life in the human body [88,92]. Bacteriocins selectively target pathogens, but not commensal microbiota [87], and present cytotoxic activity against cancer cells [95,96]. Finally, certain bacteriocins exhibit anti-inflammatory and immunomodulatory properties, thus participating in the maintenance of a balanced crosstalk between gut microbiota and immunity [90] (Figure 1).

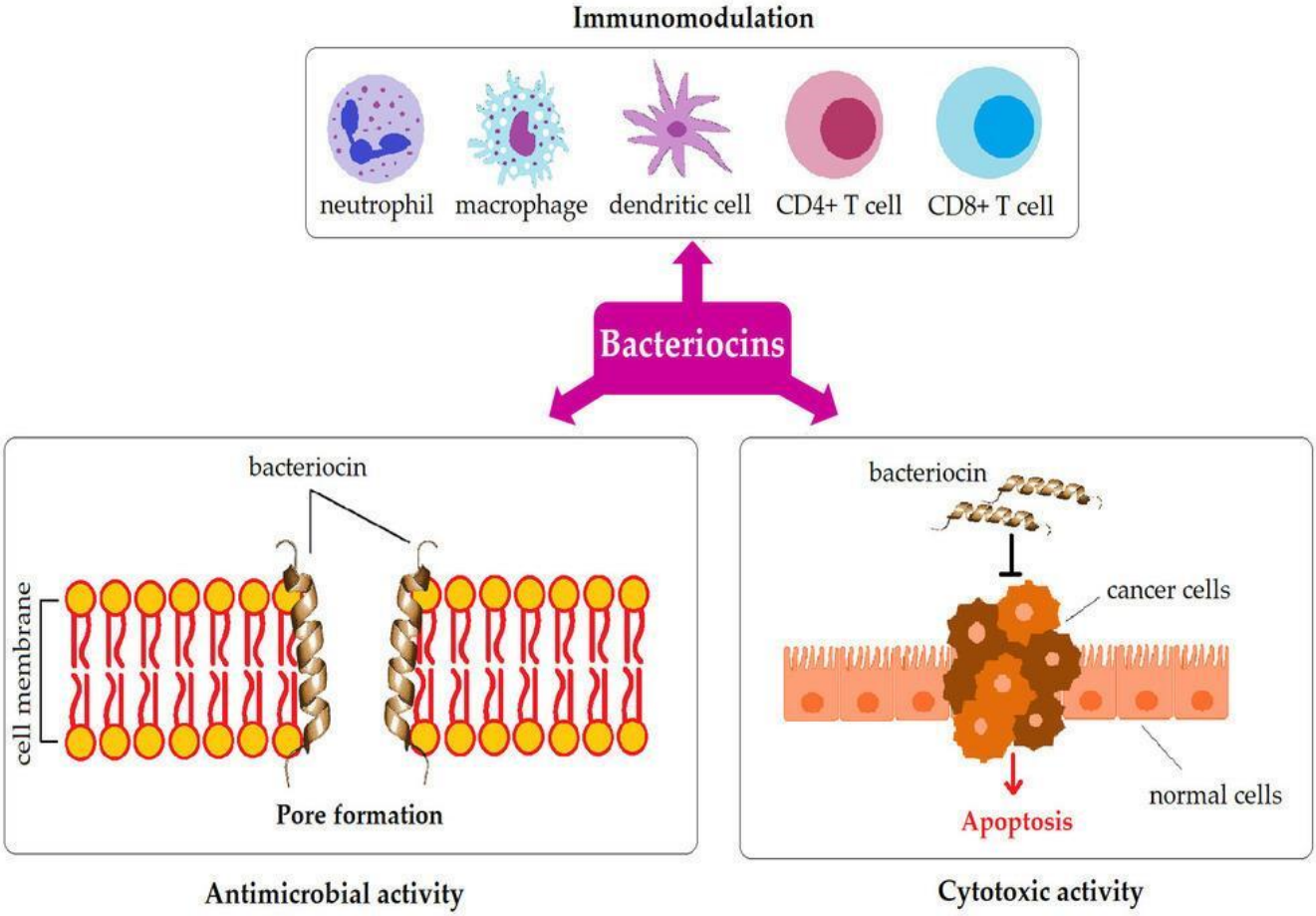

Figure 1. Bacteriocins mechanism of action.

5.1.2. Classification of LAB Bacteriocins

Bacteriocins of LAB are currently categorized into three major classes [97,98] based on their size, structure, and biochemical composition (Figure 2). Class I bacteriocins (lantibiotics) are small-sized (<5 kDa), membrane-active peptides with extensive post-translational modifications, containing uncommon dehydrated amino acids and displaying stability to heat, pH, and proteolysis [87]. Class I includes Subclass Ia, Subclass Ib, and Subclass Ic [21,86,87]. Class I bacteriocins use the peptidoglycan cell wall precursor lipid II as a docking molecule and induce pore formation on the target cell membrane to penetrate the phospholipid bilayer, leading to ion efflux and death. Additionally, they can disrupt the cell wall biosynthesis [92,94]. Class II bacteriocins are small (<10 kDa), heat-stable, non-lanthionine-containing peptides that mainly cause permeabilization of the target cell membranes [87]. This group is subdivided into four subclasses, namely Subclass IIa, Subclass IIb, Subclass IIc, and Subclass IId [21,86,87]. Class II bacteriocins, following docking on the mannose permease of the phosphotransferase system (Man-PTS), create intrinsic channels on the target cell membrane, allowing ion diffusion and leading to cell death [87,94]. Class III bacteriocins are larger (>30 kDa), heat-labile peptides and are subdivided into subclass IIIa (bacteriolysins) and subclass IIIb (non-lytic peptides) [21,87]. Their antimicrobial activity correlates with their endopeptidase enzymatic activity, leading to loss of the bacterial cell wall integrity [87,96].

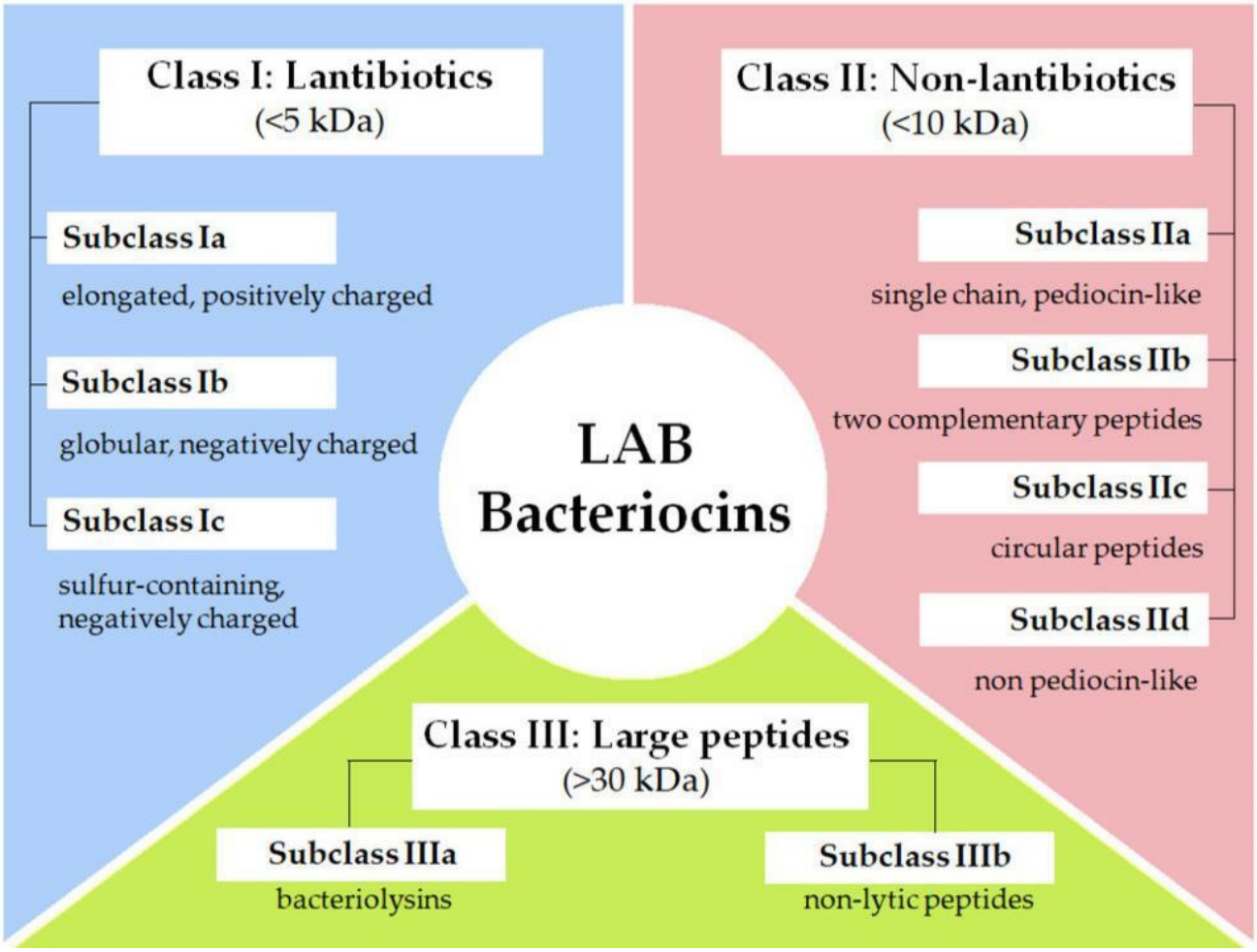

Figure 2. Classification of LAB bacteriocins.

5.1.3. Bacteriocins as Immunomodulatory Molecules

Although the immunomodulatory properties of bacteriocins have not been completely elucidated, their role as signaling peptides [99] affecting host immunity has been reported [91] (Table 1). A recent study has shown that bacteriocins, including nisin A, plantaricin 423, and bacST4SA, can migrate across endothelial and epithelial cells in vitro without causing toxicity, and they display stability in blood plasma [100]. The above observations provide strong evidence which supports the ability of bacteriocins to cross the gut–blood barrier, thereby affecting local and systemic immunity [101]. It is also suggested that bacteriocins may contribute to the stimulation of IECs which, in turn, produce antimicrobial substances to eradicate the colonization of intruding pathogens [90].

Researchers have mainly focused their interest on how nisin, a lantibiotic used in food preservation (E234), commercially available as Nisaplin [87], may affect immune responses [20]. Nisin was found to promote the production of anti-inflammatory cytokines at the expense of pro-inflammatory cytokines to inhibit inflammation in vivo [102]. Additionally, investigations on the effect of nisin on the immune system of mice showed that short-term nisin consumption induces an increase in the number of CD4+ and CD8+ T cells, as well as a significant reduction in the percentage of B cells. Following long-term nisin-consumption, T cells and B cells return to normal levels, and the population of macrophages/monocytes isolated from peripheral blood increases [103]. Similarly, a recent study which evaluated the effect of various nisin concentrations on porcine peripheral blood mononuclear cells (PBMC) in vitro, found that a high dose of nisin induces the proliferation of CD4+ and CD8+ T cells and the secretion of IL-1β and IL-6 in PBMCs, thus indicating the

enhancement of immune response against potential infections [104]. Moreover, the nisin Z variant can promote the secretion of the chemokines monocyte chemoattractant protein-1 (MCP-1), IL-8, and growth regulated oncogene-alpha (Gro-α), as well as suppress the production of tumor necrosis factor-alpha (TNF-α) in human LPS-stimulated PBMCs [105]. Nisin can also enhance the function of phagocytes that comprise an important part of innate immunity, including neutrophils and macrophages. Nisin activates the formation of neutrophil extracellular traps (NETs) by neutrophils in vitro [106], a process probably attributed to the increased production of IL-8 [107], and therefore inhibits pathogen infiltration in host cells. Treating macrophage cells with a synthesized nanoparticle containing nisin was shown to increase the levels of IL-12 without causing any effects on IL-10 and TNF-α levels [108].

Generally, bacteriocins have the ability to modulate the cytokine levels via controlling various signaling cascades (e.g., TLR, NF-κB, MAPK) in order to exert their immunomodulatory properties in case of inflammation [90]. It is reported that bacteriocins can elicit innate immune response upon viral infection via the inflammasome activation [109]. Sublancin, an antimicrobial peptide originated from *Bacillus subtilis*, was found to stimulate innate immune response via IL-1β, IL-6, TNF-α, and nitric oxide (NO) production in both RAW264.7 cells and mouse peritoneal macrophages [110]. The enhanced phagocytic capacity of macrophages was correlated with the TLR4 and the NF-κB [111] and MAPK signaling pathways, while the oral administration of sublancin increased the number of CD4+ and CD8+ T cells in MLNs in vivo [110]. Treatment of human PBMCs with acidocin A, a pediocin-like bacteriocin, resulted in increased production of multiple cytokines and chemokines, including MIG, MCP-1, MCP-3, macrophage inflammatory protein (MIP)-1α, MIP-1β, IL-6, and TNF-α [112]. Moreover, *Lactobacillus plantarum* genes encoding production or secretion of bacteriocins [113] were reported to enhance production of IL-10 over IL-12 and possibly TNF-a induction in DCs [114] and in PBMCs [115].

Table 1. The effects of probiotic derived bacteriocins on immune cells.

Cell Type	Compound	Immunomodulatory Effect	References
IECs	Sublancin	Inhibition of NF-κB activation	[90]
	Bacteriocins	Stimulation of host immunity as signaling peptides	[13,99]
Neutrophils	Nisin	NETs formation, IL-8 production	[106,107]
Macrophages	Nisin	IL-12 increase	[108]
	Sublancin	IL-1β, IL-6, TNF-α, and NO production, TLR, NF-κB, and MAPK signaling pathways modulation	[110]
DCs	*L. plantarum* bacteriocin-like peptide	Genes encoding bacteriocin secretion enhance IL-10 over IL-12	[114]
PBMCs	Nisin	CD4+ and CD8+ T cell proliferation, macrophages/monocytes increase	[103,104]
	Nisin Z	IL-1β, IL-6, IL-8, MCP-1, Gro-α secretion, TNF-α suppression	[105]
	Acidocin A	Cytokines- chemokines production	[112]
	L. plantarum bacteriocin-like peptide	Genes encoding bacteriocin secretion enhance IL-10 over IL-12	[115]

IECs: intestinal epithelial cells, NF-κB: nuclear factor-κB, NETs: neutrophil extracellular traps, IL-8: Interleukin-8, IL-12: Interleukin-12, IL-1β: Interleukin-1β, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-α, NO: nitric oxide, TLR: Toll-like receptor, MAPK: mitogen-activated protein kinase, DCs: dendritic cells, *L. plantarum*: *Lactobacillus plantarum*, IL-10: Interleukin-10, MCP-1: monocyte chemoattractant protein-1, Gro-α: Growth regulated oncogene-alpha, PBMCs: peripheral blood mononuclear cells.

5.2. SCFAs

5.2.1. Overview of SCFAs

Specific commensal anaerobic bacteria residing in the intestinal lumen are major contributors in the fermentation of non-digestible complex carbohydrates, thus producing a great amount of SCFAs [116]. SCFAs are saturated fatty acids containing six or fewer carbon atoms, including: formate (C1), acetate (C2), propionate (C3), butyrate (C4), valerate (C5), and caproate (C6) [117]. The most abundant SCFAs found in colon are acetate, propionate, and butyrate. SCFAs are released longitudinally in the intestine in different concentrations, with a maximum level in the proximal colon (100 mM) [1,118]. The fatty acids acetate, propionate, butyrate, isobutyrate, 2-methylbutyrate, isovalerate, and valerate have been detected in human feces, in decreasing order of abundance [119]. The branched SCFAs isovalerate and isobutyrate are produced in lower amounts in the gut and have been associated with aging [120]. Members of the Firmicutes phylum mostly synthesize butyrate, while members of the Bacteroidetes phylum mainly synthesize acetate and propionate [121]. Upon production in colon, SCFAs are disseminated into the bloodstream with the aim of being delivered to distant tissues, thereby exerting their beneficial effects [122].

SCFAs exhibit distinct anti-inflammatory and immunomodulatory properties and play a fundamental role in gut homeostasis, serving as the interface between gut microbiota and immunity [123]. IECs metabolize SCFAs into acetyl coenzyme A (acetyl-CoA) via the tricarboxylic acid (TCA) cycle, thus promoting cell metabolism and acquiring the essential energy for multiple cellular functions, including proliferation and activation of immune cells [124]. Butyrate serves as the primary substrate for energy production and corresponds to approximately 60–70% of total energy consumption in IECs [125,126]. Moreover, SCFAs promote the differentiation of the goblet cells involved in the secretion of mucus, thus having a well-appreciated role in maintaining mucosal barrier integrity [3]. Collectively, SCFAs perform a great variety of functions, which include protection and restoration of the intestinal epithelial barrier [125,127], prevention of gut dysbiosis via inhibition of harmful pathogens [124,128], regulation of intestinal immunity [129,130], maintenance of a balanced crosstalk between gut microbiota and extraintestinal tissues [18], and inhibition of gut inflammation through reduction in the levels of pro-inflammatory cytokines produced by immune cells [131].

In addition to the common SCFAs produced upon microbial fermentation, the presence of lactate in the intestinal lumen is considered to be a critical indicator for the preservation of gut integrity [132]. Lactate, a short chain hydroxy-carboxylic acid examined separately from SCFAs [133,134], serves as an energy substrate for a subgroup of lactate-utilizing bacterial species [132]. Under normal conditions, it is metabolized to acetate, propionate, and butyrate via distinct biochemical pathways employed by gut microbes. Therefore, the colonic concentrations of lactate are relatively low, ranging from 5 to 10 mM, in comparison to the major SCFAs [134]. On the other hand, lactate accumulation in the gut has been associated with inflammatory gastrointestinal disorders [132,134]. Lactate is not only considered as an important intermediate in cell metabolism [135–137], but also a multifunctional signaling molecule [138] with profound immunomodulatory properties both in physiological and pathological states [139].

5.2.2. SCFAs as Immunomodulatory Molecules

SCFAs play a significant role in modulating innate and adaptive immune response (Table 2, Figure 3). They are mainly recognized by three distinct G-protein-coupled receptors (GPR41, GPR43, and GPR109A) found on the surface of host IECs. Following activation of GPRs, SCFAs can modulate various signaling cascades, including MAPK, the signal transducer and activator of transcription 3 (STAT3) and the mammalian target of rapamycin (mTOR) pathways [140].

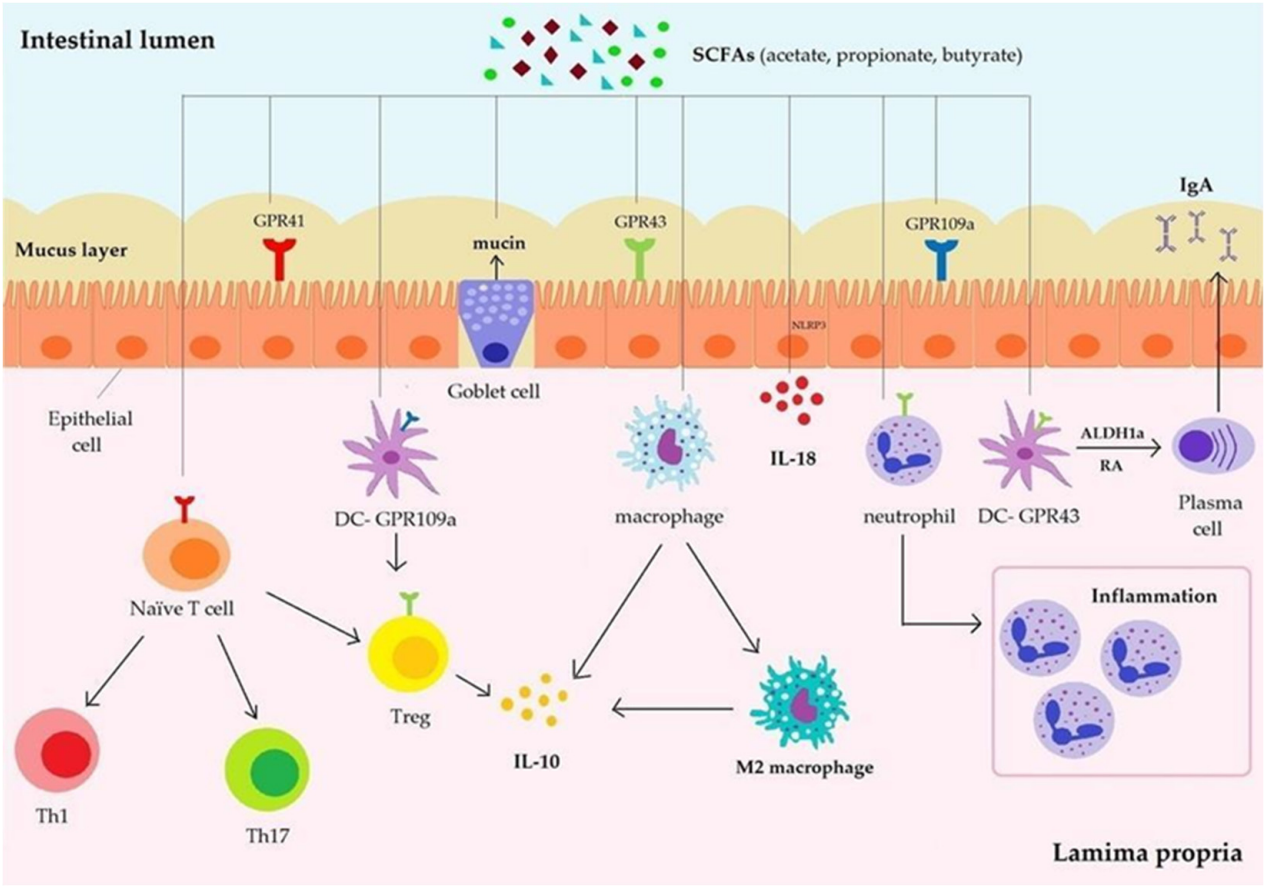

Figure 3. SCFAs modulate innate and adaptive immune cells residing in the gut. SCFAs exert their immunomodulatory properties via activation of GPRs (namely GPR41, GPR43, and GPR101A) on the IECs surface. As a result, they induce: (1) naïve CD4+ T cells differentiation towards Th1, Th17, and IL-10 producing Tregs, (2) activation of DCs, which in turn trigger IL-10 producing Tregs, (3) secretion of mucin by intestinal goblet cells, (4) M2 macrophage polarization with subsequent production of IL-10, (5) secretion of IL-18 via activation of the NLRP3 inflammasome, (6) chemotaxis of neutrophils at inflammation sites, and (7) activation of DCs which produce ALDH1a causing IgA secretion by plasma cells.

Additionally, SCFAs are involved in cell proliferation and programmed cell death via the inhibition of the enzyme histone deacetylase (HDAC) [141], and they participate in inflammasome activation, a key element of innate immune response [140]. Butyrate or acetate-GPR43-mediated signaling facilitates the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in IECs, thereby resulting in the production of IL-18, which has been linked to intestinal epithelial barrier maintenance [142]. A recent study indicated the importance of three SCFAs in restoring the reduced mucin levels in Caco-2 cells and mouse IECs previously treated with the chemotherapeutic 5-Fluorouracil (5-FU) [131]. It is speculated that SCFAs activate the NLRP6 inflammasome in order to enhance the secretion of mucin 2 by the intestinal goblet cells [1] in a similar way to other microbiota-associated metabolites [143]. Furthermore, it is reported that SCFAs inhibit the production of pro-inflammatory cytokines, including interferon-gamma (IFN-γ), TNF-α, IL-6, IL-1β, and IL-8, and they favor the production of anti-inflammatory cytokines such as IL-10 and TGF-β, via suppression of the NF-κB pathway in IECs [127,144]. Butyrate induces the activation of nuclear peroxisome proliferator-activated receptor gamma (PPAR-γ) [145], thus enhancing the β-oxidation of SCFAs and oxidative phosphorylation, contributing to the maintenance of hypoxic conditions in the microenvironment of IECs [16,17]. Under

these conditions, commensal obligate anaerobic SCFA-producing bacteria thrive, while pathogenic facultative anaerobic bacteria are eliminated [1].

The development of augmented inflammation in GPR43-deficient mice confirmed that GPR43-mediated signaling pathway leading to the activation of p38 MAPK [3] is directly associated with neutrophils chemotaxis [146,147]. Interestingly, upon exposure of LPS-stimulated neutrophils to SCFAs, the levels of NO, TNF-α, and cytokine-induced neutrophil chemoattractant-2 alpha beta (CINC-2αβ) decreased, resulting in inhibition of HDAC activity [148]. Treatment of LPS-induced THP-1 macrophages with SCFAs secreted by *E. coli* KUB-36 resulted in reduction of pro-inflammatory cytokines, and anti-inflammatory cytokine IL-10 production was triggered [149]. A recent study has also highlighted the role of butyrate in promoting M2 macrophage polarization both in vitro and in vivo in mice with dextran sulfate sodium (DSS)-induced colitis. The reduced transcription of pro-inflammatory genes in bone-marrow-derived macrophages was attributed to butyrate-induced epigenetic modulations, thus indicating the significant impact of butyrate on immune tolerance enhancement [150]. Accumulating evidence underlines the role of SCFAs in regulating the maturation and stimulation of DCs, which primarily express GPR41 and GPR109 receptors on their surface [140]. Butyrate activates GPR109A in colonic DCs, which, in turn, induces IL-10-producing Tregs, as well as the secretion of IL-18 in the intestinal epithelium of mice, providing protection against inflammation and tumorigenesis [151]. Additionally, butyrate promotes naïve T-cell differentiation to Tregs or Th1 and Th17 cells, ensuring their balance, which is a significant prerequisite to the elimination of gut inflammation [152,153]. Both butyrate and propionate were found to exert immunomodulatory properties via modulation of gene expression in DCs [154]. Supplementation with SCFAs has been proved to enhance the cytotoxic capacity of NK cells in rats while boosting the secretion of IFN-γ, the predominant cytokine produced in response to inflammatory signals [155]. Gut-associated NK cells detect invading pathogens, as well as cancer cells, and induce the recruitment of various immune cells to elicit the innate and/or adaptive immunity [140].

SCFAs are implicated in the differentiation of naïve CD4+ T cells into Tregs expressing the forkhead box protein (Foxp3) through the activation of GPR43 or GPR41 in vivo [130]. A similar increase in Tregs has been observed following oral administration of SCFAs, individually or in combination, to GF mice [156]. In vitro studies have also confirmed that butyrate and propionate favor the polarization of naïve CD4+ T cells toward IL-10+ Tregs, thus promoting resilience in the gut microbiota [140]. Upon interaction with GPR43, SCFAs activate Th1 cells and induce the mTOR and STAT3 pathways, resulting in upregulation of B lymphocyte-induced maturation protein 1 (Blimp-1) expression and IL-10 secretion in vivo [157].

Butyrate and propionate promote IFN-γ secretion, thus enhancing the cytotoxic activity of CD8+ T cells, the preponderant effector cells found in the tumor microenvironment [1,158]. Interestingly, the administration of butyrate, both in vitro and in vivo, enhanced the efficacy of the chemotherapeutic oxaliplatin via amplification of CD8+ T cell responses [159]. Moreover, the presence of SCFAs is associated with increased levels of intestinal IgA in mice. It has been confirmed that acetate activates GPR43 in intestinal DCs, thus triggering IgA secretion by B cells [1]. Alternatively, SCFA attachment to GPRs activates DCs to produce class 1A acetaldehyde dehydrogenase (ALDH1a). ALDH1a catalyzes the conversion of vitamin A into retinoid acid, thereby causing the IgA isotype switching towards secretory IgA production [1,3]. The increased energy requirements of B cells due to their multifaceted cellular processes are met by enhancement of oxidative phosphorylation and fatty acid synthesis induced by SCFAs [1,160]. Furthermore, differentiation of B cells into plasma cells in Peyer's patches is enhanced by SCFAs, which activate the mTOR pathway [160]. SCFAs employ multiple mechanisms in order to boost B cell differentiation into plasma cells and antibody production, including epigenetic regulation of specific genes such as *Aicda*, *Xbp1*, and *Irf4*, production of IL-6, and activation of Tfh cells [160,161].

Table 2. The effects of probiotic derived SCFAs on immune cells.

Cell Type	Compound	Immunomodulatory Effect	References
IECs	Acetate	GPR43 and NLRP3 activation, IL-18 production, maintenance of epithelial barrier	[142]
	Butyrate	PPAR-γ activation, β-oxidation and OXPHOS induction, conditions favoring SCFA-producing bacteria	[1,16,17]
		NF-κB pathway suppression, anti-inflammatory cytokines increase	[127,144]
	Acetate, propionate, butyrate	Restoration of mucosal barrier integrity (5-FU treated Caco-2 and IECs)	[131]
Neutrophils	Acetate, butyrate	GPR43 activation, chemotaxis induction, p38 MAPK activation	[3,146]
	Acetate, propionate, butyrate	Inhibition of ROS and NO production, NF-κB pathway suppression, HDAC inhibition	[3,148]
Macrophages	Acetate, butyrate	Pro-inflammatory cytokines reduction, anti-inflammatory cytokine IL-10 increase	[149]
	Butyrate	Epigenetic modulations, M2 macrophage polarization, immune tolerance enhancement	[150]
DCs	Butyrate	GPR109A activation, Tregs differentiation, IL-18 secretion, protection against inflammation–tumorigenesis	[151]
		Balance in Tregs and Th1-Th17 cells population, modulation of gene expression	[152]
	Acetate, butyrate	Activation of GPRs, ALDH1a production, increased secretion of IgA by plasma cells	[1,3]
NK cells	Butyrate, acetate	NK recruitment, increased IFN-γ production	[140,155]
CD4+ T cells	Butyrate	GPR43/GPR41 activation, differentiation to Tregs expressing Foxp3	[130]
	Butyrate, acetate	Th1 activation, mTOR, STAT3 pathways induction, Blimp-1 and IL-10 production	[1]
CD8+ T cells	Butyrate	Enhancement of memory CD8+ responses	[158]
		Enhancement of the efficacy of oxaliplatin, amplification of CD8+ T cell responses	[159]
B cells	Acetate, propionate, butyrate	OXPHOS- fatty acid synthesis enhancement, differentiation into plasma cells, epigenetic regulation, IL-6 production, activation of Tfh	[160,161]

IECs: intestinal epithelial cells, GPR43: G-protein-coupled receptor 43, NLRP3: NOD-like receptor family pyrin domain containing 3, IL-18: Interleukin-18, PPAR-γ: peroxisome proliferator-activated receptor-γ, OXPHOS: oxidative phosphorylation, SCFA: short chain fatty acid, NF-κB: nuclear factor-κB, 5-FU: 5-Fluorouracil, MAPK: mitogen-activated protein kinase, ROS: reactive oxygen species, NO: nitric oxide, HDAC: histone deacetylase, IL-10: Interleukin-10, DCs: dendritic cells, GPR109A: G-protein-coupled receptor 101A, Tregs: T regulatory cells, Th1: T helper 1, Th17: T helper 17, GPRs: G-protein-coupled receptors, ALDH1a: acetaldehyde dehydrogenase class 1A, IgA: immunoglobulin A, NK: Natural killer cells, GPR41: G-protein-coupled receptor 41, Foxp3: forkhead box protein, mTOR: mammalian target of rapamycin, STAT3: signal transducer and activator of transcription 3, Blimp-1: B lymphocyte-induced maturation protein 1, IL-6: Interleukin-6, Tfh: T follicular helper cells.

Lactate also exhibits a great variety of immunomodulatory properties (Table 3). Lactate plays a critical role in abrogating TLR and IL-1β dependent IECs activation [162], and it downregulates the expression of pro-inflammatory cytokines in IECs [133,136]. Interestingly, lactate has been found to induce NETs formation when administered to neutrophils [139,163]. Activation of GPR81-mediated signaling by lactate in colonic DCs and macrophages contributes to the suppression of colonic inflammation [137,164]. However, lactate can also enhance GPR81-independent metabolic changes in LPS-activated macrophages, thus inducing a reduction in pro-inflammatory cytokine levels [133,165]. Furthermore, lactate promotes M2 polarization of macrophages producing IL-10 and inhibits IL-12 production [166]. An in vitro study has also indicated that lactate is involved in the suppression of TNF-α secretion in LPS-stimulated monocytes in the tumor microenvironment (TME) [167]. The significant immunomodulatory role of lactate in TME has been extensively reviewed [168,169]. Lactate has been shown to inhibit the motility of CD4+ and CD8+ T cells [170]. In the case of CD4+ T cells it induces Th17 differentiation [168] and Tregs proliferation [171], whereas it promotes the loss of cytolytic function in CD8+ T cells [170].

Table 3. The effects of probiotic-derived lactate on immune cells.

Cell Type	Immunomodulatory Effect	References
IECs	Downregulation of pro-inflammatory cytokines	[133,136]
	Abrogation of IECs activation depending on TLRs and IL-1β	[162]
Neutrophils	NETs formation	[139,163]
DCs	GPR81 activation, suppression of colonic inflammation	[137,164]
	Cell surface markers modulation and cytokine secretion in LPS-activated DCs	[133,137]
Macrophages	GPR81-independent metabolic changes, pro-inflammatory cytokines reduction	[165]
	GPR81 activation, suppression of colonic inflammation	[137,164]
	M2 macrophage polarization, IL-10 increase, IL-12 decrease	[166]
	Downregulation of cytokine secretion in LPS-activated macrophages	[133]
Monocytes	Inhibition of glycolysis, suppression of TNF-α secretion in the TME	[167]
CD4+ T cells	Glycolysis-dependent inhibition of motility, Th17 differentiation, increased IL-17 levels	[170]
	Tregs proliferation	[171]
CD8+ T cells	Glycolysis-independent inhibition of motility, loss of cytolytic function	[170]

IECs: intestinal epithelial cells, TLR: Toll-like receptor, IL-1β: Interleukin-1β, NETs: neutrophil extracellular traps, DCs: dendritic cells, GPR81: G-protein-coupled receptor 81, LPS: Lipopolysaccharide, IL-10: Interleukin-10, IL-12: Interleukin- 12, TNF-α: Tumor necrosis factor-α, TME: tumor microenvironment, Th17: T helper 17, IL-17: Interleukin-17, Tregs: T regulatory cells.

6. Challenges and Future Perspectives

The contribution of probiotics in the maintenance of a healthy gut microbiota and a balanced interaction between commensal bacteria and immune cells is noteworthy. However, a few studies have highlighted impediments in probiotic utilization, despite their accredited beneficial effects on human health. For instance, it has been reported that probiotics administered to eliminate common treatment-related side effects in adult cancer patients led to the development of undesired health issues, including bacteremia, endocarditis, sepsis, and pneumonia [172]. Several factors could account for the initiation of inflammatory responses upon probiotic treatment, such as: significant gut microbiota variability between individuals, probiotic strain-specific function, and bacterial translocation to remote tissues or into the bloodstream [24]. Therefore, it is important to evaluate the

risk–benefit ratio prior to probiotic administration to individuals with increased intestinal permeability and immunocompromised patients. Additionally, clarification of the exact molecular mechanisms of probiotic action, selection of the appropriate bacterial strain for targeted therapy, and determination of the most efficient dose remain necessary [173].

It is hypothesized that specific probiotic-derived compounds, mainly bacteriocins and SCFAs, are involved in the improvement of gut immunity without causing the undesirable side effects related to living microorganisms in high-risk patients [51]. Bacteriocins could be a promising therapeutic approach for the eradication of harmful pathogens showing resistance to conventional antibiotics [88,174]. Nevertheless, there is limited in vitro and in vivo evidence regarding their efficacy and safety as a treatment option for various human diseases [90]. In order to determine their efficiency, pharmacokinetic parameters, including solubility, bioavailability, and biodegradation, must be evaluated [175]. A few studies have indicated that bacteriocins may aggregate in vivo due to disturbance of their physical stability or alterations of their biochemical properties during their exposure in the GI tract. This could lead to low bioactivity and a subsequent immune response [91]. In this context, the encapsulation of purified bacteriocins into a protective matrix or the application of bioengineering methods [176] could be efficient approaches in order to improve their stability when orally administrated [175]. Further studies should be conducted to determine the action of purified bacteriocins since the presence of other postbiotics may mask their actual effects, as well as the combined action of their mixtures, since probiotics produce a variety of them. Thus, it is still challenging to develop more advanced, efficient, and affordable methods for the purification of bacteriocins from cell free supernatants to ideal concentrations for therapeutic applications [176] or the discovery of new bacteriocins [177].

In general, SCFAs comprise the largest group of bioactive compounds residing in the gut lumen, thus participating vigorously in the stimulation of gut immunity synergistically with other endogenous metabolites or exogenously administered drugs [1,146]. Additionally, SCFAs are endowed with the capacity to promote immune response, not only locally, but also systemically, due to their dissemination to distant tissues and organs [18,178]. To date, there are limited in vivo studies focusing mostly on the impact of SCFAs administration in chemically induced colitis animal models. The design of randomized controlled trials is required to fully understand the clinical impact of SCFAs in host health [116]. Several factors could affect the efficacy of SCFAs, including their route of administration, their dynamic interactions with commensal bacteria or other metabolites, and the variability in gut microbiota composition between individuals. It still remains a major challenge to determine the in vivo production of SCFAs in tissues other than the gut [179]. In this context, further investigations are necessary to extrapolate conclusions regarding the optimal dose and composition of SCFAs, and comparative analysis experiments could configure the criteria of SCFAs utilization based on the distinctiveness of each individual. Finally, there is lack of evidence regarding the combined action of purified bacteriocins and SCFAs. Further studies are warranted to ascertain their optimal ratio as therapeutics.

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