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Review article

Microbiota substances modulate dendritic cells activity: A critical view

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ABSTRACT

Contemporary research in the field of microbiota shows that commensal bacteria influence physiological activity of different organs and systems of a human organism, such as brain, lungs, immune and metabolic systems. This influence is realized by various processes. One of them is trough modulation of immune mechanisms. Interactions between microbiota and the human immune system are known to be complex and ambiguous. Dendritic cells (DCs) are unique cells, which initiate the development and polarization of adaptive immune response. These cells also interconnect native and specific immune reactivity. A large set of biochemical signals from microbiota in the form of different microbiota associated molecular patterns (MAMPs) and bacterial metabolites that act locally and distantly in the human organism. As a result, commensal bacteria influence the maturity and activity of dendritic cells and affect the overall immune reactivity of the human organism. It then determines the response to pathogenic microorganisms, inflammation, associated with different pathological conditions and even affects the effectiveness of vaccination.

1. Introduction

Scientific projects Metagenomics of the Human Intestinal Tract Consortium (MetaHIT) and the Human Microbiome Project (HMP) using genetic research methods have significantly clarified knowledge about the species richness, amount, and importance of bacteria inhabiting a human body [1–3]. Previously, it was accepted that bacteria are present only on the skin and mucous membranes. It is now known that through some types of tissues that have the ability to flow (phenomenon of "leaky gum" and "leaky gut") [4,5] bacteria and their metabolites can enter the circulation [6], and from there – various organs and tissues and be an important component of the tissue microenvironment [7–10]. Some organs in mammals, for example, the mammary gland, have unique, not yet fully studied mechanisms of bacterial transport from the intestine [11,12]. During the development of pathological processes in tissues that contacts with commensal bacteria, a change in the composition and metabolic activity of microbiota is observed [13–16]. For the long process of

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evolution, commensal bacteria fully adapted to life in the human body and play an integral important role in common metabolic processes as unique and special "metabolic organ" [17,18].

Therefore, commensal bacteria are widely represented in the human body. They are constantly in contact with the cells of the immune system and affect the mechanisms of the immune response. In many studies of the immune system in germ-free animals, it has been shown that the immune system in the conditions of development of animals without microbiota is anatomically and functionally underdeveloped [19–21]. Generally, it has been calculated that the number of species of human commensal bacteria is approximately 10,000 [22]. At the same time, about 1500 species of pathogenic bacteria have been reported up to date [23]. Throughout life, the human body comes into contact with around one thousand commensal bacteria as well as several dozens of pathogens. Therefore, the human organism and its immune system are mostly in contact with commensal bacteria. Many of them are opportunistic and could induce the development of an infectious process in some circumstances. Thus, microbiota is considered to educate the immune system. It has been shown that, by artificially changing the microbiota composition in animals, it was possible to influence the mechanisms of the anti-infectious immune response [24] and even the effectiveness of vaccination [25].

The main idea of this review is to analyze the impact of some substances produced by commensal bacteria on human dendritic cells (DCs) in *in vitro* and *in vivo* studies, focusing on co-stimulatory molecule expression, cytokine production, and the induction of effector T cell differentiation. Different bacterial substances, such as cell wall components lipopolysaccharide (LPS) [26,27] or peptidoglycan (PGN) [26], and bacterial metabolites, such as short chain fatty acids (SCFAs) [28], secondary bile acids (SBAs) [29], bacterial autoinducers, demonstrated diverse and sometimes opposite effects on DCs [30]. Therefore, DCs have to integrate different biochemical signals from bacteria to generate the most appropriate "answer". In addition, DCs have to sense other signals from environment, such as cytokines, contacts with other cells, and extracellular matrix. The state of activation of DCs by this complexity of signals further affects the direction and nature of the immune reactions developed.

2. Dendritic cells. Key functions and significance

Historical reference shows that Paul Langerhans first discovered DCs in the skin in 1868. Due to their special process-like morphology, the scientist attributed them to a special type of nerve cells [31]. These cells received the name "Langerhans cells", which has been preserved to this day. For a long time, the scientific community was not aware of these cells. Only more than 100 years later, in 1973, at a conference in Lieden, devoted to mononuclear phagocytes, a young scientist Ralph Steinmann gave a report on special cells isolated from the spleen, which constituted only 1% of all splenocytes and had some properties similar to macrophages [32]. These cells were first called "dendritic cells". Ralph Steinmann dedicated his entire scientific life to the study of DCs and made many discoveries in this field, which were awarded the Nobel Prize in 2011.

DCs are considered to be gatekeepers of the immune system, and contact between them and microbiota is essential for proper immune system development and regulation. Resident DCs are found in various organs and tissues. They have embryonic origin and are capable of self-renewal. If necessary, peripheral blood monocytes can differentiate into DCs when they get into tissues.

We now know that there are many populations of DCs depending on their origin, localization and functions [33,34]. Two types of DCs are the most well-known – conventional DCs (cDCs) and plasmacytoid DCs (pDCs). Conventional DCs could be subdivided into two groups of cDC1s and cDC2s, which have distinct transcriptional programs and functional properties. Human and murine DC subsets are similar in subset development and activity of transcription factors; nevertheless, they have some differences in surface markers expression [35]. The functions of cells in different populations are also somewhat different.

However, all DCs have common features – they are professional antigen-presenting cells (APCs), which nonspecifically intake various antigenic material (microorganisms, remnants of eukaryotic cells, etc.), process engulfed antigens and present them in a complex with MHC I, MHC II molecules or other MHC-I-like molecules (CD1) in secondary lymphoid organs for priming of naive αβT-cells or activation of NK-T and γδT cells [36]. Generally, mature DCs represent several key activating surface ligands or secreted factors to naive T cells to prime and activate them. Among them there are: antigenic peptide-MHC complexes (signal 1), costimulatory molecules CD80/86 (signal 2), and cytokines (signal 3). The nature of antigen, microenvironmental stimuli, the type of DCs and state of their maturation very greatly influence the polarization of adaptive immune response with the formation of T cell effector populations: Th1, Th2, Th17, or Treg.

During development from immature to mature cells DCs show different ability to respond to bacterial substances. DCs precursors with high phagocytic function most actively express receptors for recognition of bacterial molecular patterns. For example, immature CD11c + DCs express TLR 1, 2, and 3, while progenitors of pDCs exhibit significant expression of TLR7 and 9. This indicates that DCs of different populations are tuned to detect different substances of microorganisms and further trigger multidirectional immune reactions.

Resident DCs in tissues are immature and characterized by pronounced phagocytic activity but low levels of expression of costimulatory molecules CD80, CD86, CD83, CD40, OX40L, and ICOS-L and lack of cytokine secretion. DCs mature after intake of foreign antigens and interaction with certain bacterial substances. Mature DCs are distinguished by the absence of phagocytosis, high expression of costimulatory molecules, and secretion of cytokines.

Therefore, DCs, depending on their type, state of maturity and produced cytokines, can induce a wide range of immune response reactions with the involvement of different populations of effector cells, which are generally aimed both at removing the antigen from the body and maintaining mechanisms of immune tolerance to a certain antigen [37]. In addition, DCs is an important connecting link between natural and adaptive immunity [38]. Due to their important role in initiating the adaptive immune response, DCs are used for the creation of vaccines [39].

Differentiated human DCs, which can be isolated from tissues, do not grow well *in vitro*. Therefore, the most common and

convenient approach to obtaining human DCs *in vitro* is the induction of maturation in peripheral blood monocytes. Peripheral blood mononuclear cells are obtained by centrifugation in a density gradient (ρ = 1.077). Next, monocytes are separated using various technologies that take into account the ability to stick to plastic or the expression of the monocyte marker CD14 [40]. Monocytes are further stimulated with such cytokines as granulocyte monocyte colony stimulating factor (GM-CSF) and interleukin-4 (IL-4) and grown for a week. In this way, immature human DCs of monocytic origin are obtained [41]. There are several protocols for obtaining mouse DCs for *in vitro* experiments. According to one of the protocols, bone marrow derived DCs (BM-DCs) were prepared from bone marrow suspensions obtained from the femurs and tibias. In order to obtain immature DCs, bone marrow cells were cultured with murine GM-CSF [42].

In standard protocols for growing DCs *in vitro* for induction of maturity, immature DCs are usually treated with *E. coli* LPS [43]. In the case of growing DCs for the creation of antitumor vaccines, the DCs are further loaded with a tumor antigen [26]. After these manipulations, the maturity of the obtained DCs must be determined. In order to do so, the expression of DCs surface markers, including HLA-DR, CD80, CD86, and CD40, as well as cytokine secretion, are measured. The protocol for growing DCs *in vitro* corresponds to the situation *in vivo* because immature DCs located in tissues actively engulf antigens and move to T-dependent zones of peripheral lymphoid organs. Simultaneously, DCs mature, exhibiting high expression of MHC and costimulatory molecules. They effectively present antigens to specific T-cells and influence the differentiation of these cells. Over millions of years of evolution, the immune system has developed highly efficient mechanisms for responding to pathogens and commensal bacteria. These mechanisms are initiated when immune sentinel cells, such as DCs, recognize bacterial molecular patterns. Furthermore, the initial recognition of bacterial substances by DCs influences both DC maturation and the polarization of the immune response [44].

3. Microorganism associated molecular patterns and DCs interaction

Any commensal or pathogenic bacteria are carriers of both genetically foreign information and a large number of antigenic structures. These unique antigenic structures, absent in eukaryotic organisms, are generally called microorganism associated molecular patterns (MAMPs), or pathogen associated molecular patterns (PAMPs). By biochemical structure, PAMPs traditionally include peptides, polysaccharides, lipid structures of the cell wall, intracellular proteins, as well as the DNA and RNA of bacteria (Fig. 1). Recognition of these bacterial antigens by DCs occurs with the participation of a number of membrane and intracellular conserved receptors, generally called pattern recognition receptors (PRRs). The idea of PRR was first proposed and developed by Charles Janeway in 1989 [45]. The most well-known types of receptors include membrane Toll-like receptors (TLR), C-type lectin receptors (CLR), intracellular NOD-like receptors (NLR), and RIG-like receptors (RLR) [46]. Each type of receptor has many molecular variants that interact with various substances of microorganisms and initiate the development of the corresponding signaling cascades.

Therefore, it is traditionally accepted that the molecular patterns of bacteria include such substances that are actually components of the bacterial cell and confirm the presence of bacteria as such. Bacterial metabolites and their corresponding receptors are currently not considered within the framework of generally accepted MAMPs and PRRs. In our opinion, there should be a certain clarification in this topic because such bacterial metabolites as SCFAs, SBAs, and autoinducers (AIs) are extremely conservative molecules in evolutionary terms. They are produced only by bacteria and, like LPS and PGN, are a biochemical "bar code" of actively communicating and metabolizing living bacteria. Thus, the presence and concentration of these molecules indicates not only the presence of bacteria, but also the state of their metabolism and behavior as a population. They could be called Microorganism Metabolism

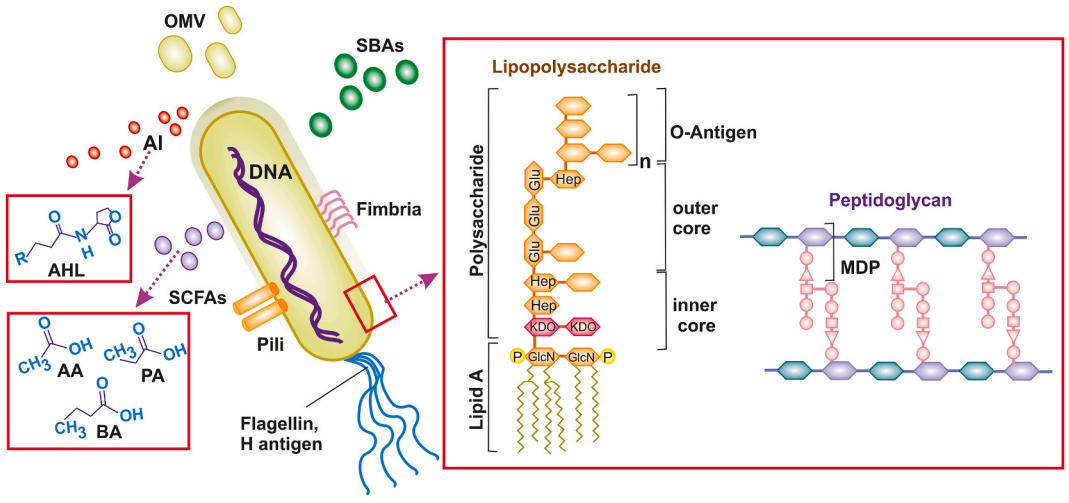

Fig. 1. Bacterial MAMPs, metabolites, and cellular components. OMV – outer membrane vesicles, SCFAs – short chin fatty acids, AA – acidic acid, PA – propionic acid, BA – butyric acid; SBA – secondary bile acids; AI – autoinducers, MDP – muramyldipeptide, AHL – acyl homoseryne lactone. Residues are indicated as hexagons: GlcN, glucosamine; Kdo, 3-deoxy-D-manno-oct-2-ulosonic acid; Hep, L-glycero-dmanno-heptose; Gal, Galactose; Glu, Glucose. Phosphate groups are indicated as circled P.

Associated Molecular Patterns (MMAMPs).

In this review, we will focus on some of the most studied molecular antigenic patterns of bacteria, such as bacterial cell wall components, like PGN and LPS. PGN is a cell wall component of all bacteria that have a cell wall at all [47]. LPS is present in the cell wall of gram-negative bacteria. As a result of shedding from the surface or destruction of bacterial cells, for example, in the intestine, these substances can be detected in the bloodstream and introduced into various organs and tissues [48]. Then, PGN and LPS systemically affect the activity of the immune system.

In reviewed literature of *in vitro* studies, scientists obtained immature DCs from human peripheral blood monocytes by incubation with cytokines (IL-4, GM-CSF). Murine immature DCs were obtained from bone marrow myeloid progenitors followed by GM-CSF treatment or conventional DC isolation from spleen tissue. Next, immature DCs were treated with bacterial substances and the effect on the state of maturity, secretory activity of DCs and, in some cases, on the polarization of the immune response at the level of effector T cells was determined. For this, DCs were incubated with autologous or allogeneic naive $CD4^+$ T lymphocytes, and then the functional activity of these effector lymphocytes was determined.

3.1. PGN interaction with DCs

PGN is a key biopolymer of bacterial cell walls. The basic structure of PGN contains linear glycan chains (made out of alternating β-1,4-connected N-acetylglucosamine, GlcNAc and N-acetylmuramic acid, MurNAc residues), which are cross-linked by short pentapeptide chains (Fig. 1). Pentapeptide chains contain L- and D-amino acids, whereby the latter is characteristic of bacterial PGN [47]. Bacterial peptidoglycans of different species are somewhat dissimilar in their biochemical structure and antigenic properties.

In most *in vitro* studies, PGN from an opportunistic bacterium, *Staphylococcus aureus*, was used to treat DCs. Results of studies listed in Table 1 show that PGNs of bacteria of different species has slightly different effects on the state of maturity and functional activity of human DCs. For example, *S. aureus* PGN stimulated the maturation of DCs and increased their expression of molecules related to antigen presentation (HLA-DR, CD80), costimulatory molecules (CD40) and receptors necessary for migration to T-dependent zones of secondary lymphoid organs (CCR7). Also, stimulated with *S. aureus* PGN DCs produced pro-inflammatory cytokines IL-1β, IL-6 and IL-23 [48,49]. These DCs further stimulated the development of naive CD4+T lymphocytes in Th17 in the *in vitro* system (Table 1). *In vitro* studies using DCs of mouse origin showed that *S. aureus* PGN also contributes to the maturation of DCs and increased expression of such surface markers as MHC II, CD80, and CD86 [50]. The production of pro-inflammatory cytokines IL-12p70 and TNF-α by DCs, as well as anti-inflammatory cytokine IL-10 were detected. This DCs phenotype led to the polarization of the immune response in the direction of Th1 formation. It is quite understandable and confirmed by research data that the key mechanism of the immune response to destroy *S. aureus* is the phagocytosis of bacteria with the participation of neutrophils and macrophages. These natural immune responses are greatly enhanced by Th17 and Th1, respectively.

Table 1
Human and mice DCs, stimulated with PGN and LPS *in vitro*.

Bacterial substances	DC maturation	T cell polarization and produced cytokines	Ref
Peptidoglycan (PGN)			
PGN *S. aureus*		Th17	[26]
PGN *S. aureus*	hMDDC: HLA-DR↑, CD83↑, CD40↑, CD86↑, CCR7↑, IL-23↑, IL-6↑, and IL-1β ↑,	IL-17↑, IL-21↑,	
PGN *L. rhamnosus*	(not IL-12p70)		
PGN *S. aureus*	hMDDC: IL-23↑, IL-6↑, IL-10↑, IL-12↓	Th17	[43]
PGN *S. aureus*	hMDDC: CD86 ↑, TNF-α↑		[46]
PGN *S. aureus*	hMDDC: CD86 ↑, HLA-DR↑, CD83↑		[50]
PGN *S. aureus*	hMoLC: CD86 ↑, HLA-DR↑, CD83↑		[50]
PGN *S. aureus*	mBM-DC: low IL-12p70↑, IL-10↑, TNF-α↑	Th1	[47]
PGN *S. aureus*	mBM-DC: MHC II↑, CD80↑, CD86↑		[44]
PGN *S. gordonii*	mBM-DC: MHC II↑, CD86↑		[48]
	murine Langerhans cells: CXCL10↑, CCL17↑		[49]
	mBM-DC: CD80↑, CD86↑, TNF-α↑, IL-6↑, IL-10↑		[45]
Lipopolysaccharide (LPS)			
LPS *E. coli*	hMDDC: CD86 ↑, HLA-DR↑, CD83↑		[27]
LPS *E. coli*	hMDDC: HLA-DR↑, CD86↑, CD40↑		[51]
LPS *E. coli*	hMDDC: CD86 ↑, HLA-DR↑, ICOS-L↑ PDL1↑, PDL2↑, TNF-α↑, IL-6↑, IL-10↑,		[52]
LPS *P. gingivalis*	IFN-γ↑, IL-2↑		
LPS A. actino	hMDDC: HLA-DR↑, CD80 low↑, CD40 low↑, CD83 low↑, low TNF-α↑, low IL-	Th2,	[53]
mycetemcomitans	10↑	IL-13, IL-5	[53]
LPS *E. coli*	hMDDC: HLA-DR↑, CD80↑, CD40↑, CD83↑, low TNF-α↑, low IL-10↑	Th1, high IFN-γ, IL-2, but less IL-5	[53]
	hMDDC: HLA-DR↑, CD80↑, CD40↑, CD83↑, TNF-α↑, IL-10↑, IFN-γ↑, induction		[54]
LPS *P. gingivalis*	of Th1 development		[54]
LPS *E. coli*	hMDDC: low TNF-α↑, low IL-10↑,		[55]
	hMDDC: IL-12 p70↑, IP-10↑, TNF- α↑, IL-10↑, IL-6↑, IL-1 β↑		
LPS *E. coli*	hMDDC: CD83↑, CD209↑, IL-6↑, IL-12p40↑,		

Human Monocyte-derived DC (hMDDC), mice Bone Marrow derived DC (mBM-DC), human Monocyte-derived Langerhans like cells (hMoLC), IFN-γ-inducible protein 10 (IP-1).

It has been shown that PGN of oral microbiota commensal *Streptococcus gordonii* induced an increase in the expression of CD80 and CD86 on mouse BM-DCs, and also promoted the secretion of IL-6, TNF-α, and IL-10 [56]. In the same study, it has been shown that whole bacterial cells, inactivated by UV, were more effective in stimulating the surface markers of DCs maturity and their production of cytokines. In addition to the cytokines listed above, BM-DCs treated with whole bacterial cells also produced IL-12p70 [56].

A slightly different effect was observed when treating human MDDCs with PGN of *Lactobacillus rhamnosus*. The expression of HLA-DR, CD80 and CD83 markers did not change on DCs. However, CD86 expression and TNF-α secretion increased [57].

In general, when DCs were treated with peptidoglycans of different types of bacteria *in vitro*, it was found that DCs acquire a more mature phenotype, highly express surface markers HLA-DR, CD83, CD86, CCR7 and secrete cytokines TNF-α, IL-6, and IL-1β (Table 1) [58–61]. PGN-treated DCs further promoted the formation of Th1 or Th17, which are effector cells of pro-inflammatory specific immune responses (Fig. 2).

In the human organism, DCs can interact with pure PGN, which is formed as a result of the active growth or destruction of bacterial cells. For example, it was investigated that during *S. aureus* infection in the exponential phase of growth, PGNs are exfoliated, which contributes to the activation of DCs and the polarization of the immune response in the direction of the development of Th17-dependent pro-inflammatory mechanisms [48]. At the same time, PGN inhibited the production of IL-12 by DCs [62] and the polarization of the immune response in the direction of Th1 formation [48]. Th17-dependent immune responses involving activity of neutrophils are necessary to eliminate extracellular pathogens. When *S. aureus* is in a stationary phase of growth or the bacteria are inside eukaryotic cells, this leads to skewing of immune system mechanisms to Th1 cell polarization, which are necessary for the destruction of intracellular internalized bacteria [48].

Lisbeth Drozd Lund et al. showed that *S. aureus* in the early exponential growth phase stimulated the production of IL-12, TNF-α, and IL-10 in mice DCs. Bacteria in the stationary growth phase were less effective DC cytokine synthesis and secretion inducers. Ultraviolet light (UV)-killing of bacteria also reduced their ability to induce DC cytokine secretion. It has been shown that only intact *S. aureus* bacteria in the exponential phase of growth induced IL-12 secretion by DCs. Killing the bacteria with UV partially reduced, but did not abolish the production of all cytokines, including IL-12. The maximum level of expression of CD86 and CD40 was also observed when DCs were treated with intact bacteria [62]. *S. aureus* mutants that do not produce poly-N-acetyl glucosamine (PNAG) were shown to induce greater IL-12 production by DCs compared to wild-type strains [62]. Therefore, it is obvious that the immune reactions that develop in a healthy organism are maximally adapted not only to bacteria as such, but also to the growth phases of these bacteria in case of development of an infectious process.

When carrying out such research, several points draw attention. Firstly, the ability of PGN to induce pro-inflammatory immune responses depends on the structure of the biopolymer. It has been shown that, in case of changes in the structure of PGN by bacteria as a result of changes in the activity of genes responsible for biochemical modifications of PGN, alterations in immune response reactions are also observed. For example, impaired activity of the enzyme glucosaminidase SagB [63] or O-acetylation of PGN in *S. aureus* [64] results in production of PGNs that impair effective maturation and development of proinflammatory functions of DCs. Bacteria usually use such mechanisms to avoid the host's immune response.

Secondly, when interpreting the results of experiments with the co-cultivation of DCs and lymphocytes, it is necessary to understand that DCs receive an additional activation stimulus from lymphocytes through the CD40 molecule. In this case, MAMPs and CD40 ligation have a synergistic effect. Therefore, in some studies, scientists separately investigated this point using the CD40 ligand [61].

Thirdly, the expression of certain sets of PRRs differs in various populations of DCs; therefore, DCs of different types respond in a distinctive way to the same MAMPs. The experiment with human MDDCs and MoLCs showed that under the same conditions of

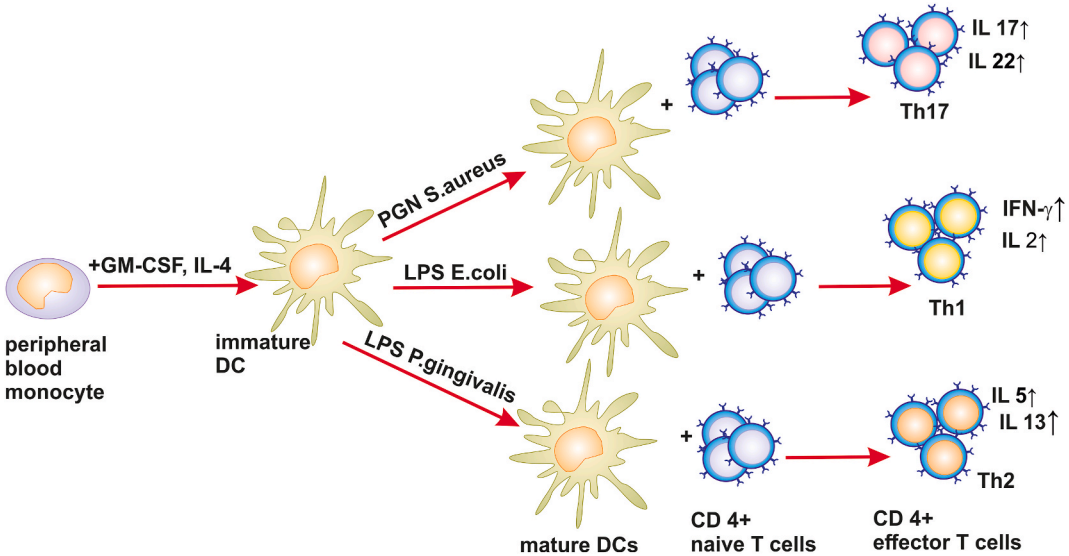

Fig. 2. Scheme of LPS and PGN influence DCs maturation and function *in vitro*.

stimulation with PGN and CD40 ligation, the expression level of CD80 and CD83 was higher on MDDCs. In addition, the level of expression of receptors interacting with the molecular patterns of bacteria changes during the differentiation of DCs from monocytes. For example, the expression level of TLR2 and TLR4 is significantly reduced [65], which indicates a certain "window of opportunity" for responding to bacterial antigens at certain early stages of DCs development. This state of maturity corresponds to the stage of DC presence in tissues. After engulfment of antigens in tissues, movement to T-dependent zones of secondary lymphoid organs and presentation of antigens there, DCs acquire a mature phenotype necessary for effective activation of naive T cells.

Thus, in most *in vitro* experiments bacterial PGN showed the ability to induce pro-inflammatory activity of DCs.

3.2. Interaction of DCs with LPS

LPS is a component of gram-negative bacteria cell walls that support its integrity. According to the chemical structure, LPS is a complex structure composed of Lipid A, core oligosaccharide and side O-antigen moieties (Fig. 1). It is localized in the external part of the bacterial outer membrane (OM). LPS is one of the major virulence factors and plays a crucial role in host-pathogen interaction by modulating the innate immune response [66,67]. LPS is also called endotoxin, the toxicity of which is mainly related to lipid A. Lipid A is the most conserved part of the LPS molecule. Bacteria of different species have peculiarities in the structure of lipid A and polysaccharide components. The differences in lipid A mainly relate to the length and number of acyl chains [68]. The core oligosaccharide part of LPS is divided into inner and outer core. Inner core is more conservative, but outer core is variable. The inner core contains at least one residue of 3-deoxy-D-manno-oct-2-ulosonic acid (Kdo). It links the inner core to lipid A, and usually also L-glycero-D-manno-heptose (heptose) [68]. The O-antigen is composed of repeating units of one to six different residues. They form the distal surface-exposed LPS moiety responsible for the immunogenic properties of this macromolecule (Fig. 1). It is the most variable portion of LPS. Different bacterial strains could be distinguished by specific antisera to certain O-antigens [52].

LPS is one of the most famous MAMPs, the history of LPS investigation has been for more than 150 years [27]. LPS lipid A interacts with the TLR4 receptor and auxiliary molecules LBP, CD14 and MD2 on cells of innate and adaptive immunity, epithelial cells [51]. Activation of TLR 4 on DCs leads to the higher expression of co-stimulatory molecules and synthesis of pro-inflammatory cytokines and chemokines. *E. coli* LPS was mostly used in *in vitro* studies to investigate the effect of LPS on DCs. It should also be noted that standard schemes for preparation DCs *in vitro* from peripheral blood monocytes for the purpose of immunotherapy of oncological diseases include treatment with *E. coli* LPS as a pro-inflammatory activating stimulus [43,55].

Changes in the metabolic profile of DCs after treatment of human MDDCs with *E. coli* LPS *in vitro* have been investigated [53]. The time-dependent character of activation of some metabolic pathways in DCs has been found. The most affected were TCA cycle, nucleotides, nucleotide sugars, and polyamines pathways and, to a lesser extent, the arginine pathway [53].

In experimental studies, it was shown that the duration of exposure and the concentration of applied LPS had different effects on the activation of MDDCs [54,69–72]. In one of the study authors found that B7 costimulatory molecules express differently in response to different LPS concentrations and stimulation times [69]. They observed the expression of the coinhibitory molecules PD-L1 and PD-L2 at an early stimulation time and under low antigen concentrations. Meanwhile, the costimulatory molecules CD86 and ICOS-L express at late times (48 h) regardless of the antigen concentration. Also, they found that increased production of TNF-α, IL-6, and IL-10 was observed at early times of stimulation with LPS (12 h and 24 h), which may influence the PD-L1 and PD-L2 expression. In contrast, cytokines related to T-cell activation, IFN-γ and IL-2, had a maximum secretion peak at the most prolonged time evaluated (48 h), similarly to the CD86 and ICOS-L expression [69]. Therefore, the dynamics of the expression of activating and inhibitory markers and the secretion of DC cytokines depend on the duration of contact with the antigen and its concentration, which can be controlled only under the conditions of *in vitro* experiments.

The effect of LPS obtained from *E. coli* and the periodontal pathobionts *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* on DCs of human monocytic origin was compared in Rangsini Mahanonda et al. investigation [73]. It was shown that all three types of LPS up-regulated expression of HLA-DR, CD40, CD80, and CD83 on MDDCs in a dose-dependent manner. *A. actinomycetemcomitans* LPS and *E. coli* LPS induced similar levels of these surface molecules, and these levels were consistently higher than those induced by *P. gingivalis* LPS. With regard to LPS-induced cytokine production, it was found that both periodontal pathobionts LPSs induced low levels of TNF-α and negligible amounts of IL-10 from MDDCs. In contrast, *E. coli* LPS induced substantial levels of TNF-α and moderate amounts of IL-10 [62]. LPS from three bacterial species induced minimal or no IL-12 p70 production. When studying the ability of MDDCs to induce the differentiation of naive CD4+T cells, it was found that LPS obtained from *P. gingivalis* and *A. actinomycetemcomitans* showed much less activity compared to *E. coli* LPS.

Ravi Jotwani et al. showed that *E. coli* LPS-pulsed human MDDC released Th1-biasing cytokines consisting of high levels of IL-12 p70, IFN-inducible protein 10 (IP-10), TNF- α, IL-6, IL-1β, and IL-10 [74]. In contrast, no IL-12 p70 or IP-10, and lower levels of TNF-α and IL-10 were observed after MDDCs were induced by *P. gingivalis* LPS. Investigation of allogenic naive T cell response was consistent: *E. coli* LPS-pulsed MDDC induced higher T cell proliferation, and T cells released more IFN-γ and IL-2, but less IL-5 than T cells co-cultured with *P. gingivalis* LPS pulsed-MDDC. In addition, IL-13 was secreted by naive CD45RA + CD45RO– $CD4^+$ T cells in response to *P. gingivalis* LPS-pulsed MDDC. These results suggest that LPS from the periodontal pathogen *P. gingivalis* could polarize human MDDC to induce a Th2 effector response *in vitro*.

Therefore, in a series of *in vitro* studies, it was shown that human MDDCs treated with LPS of different types of bacteria induce the formation of diverse types of effector T cells and drive the development of the immune response in different directions. Thus, *E. coli* LPS stimulated MDDCs to activate Th1 formation, while *P. gingivalis* LPS promoted the development of another phenotype of MDDCs with subsequent activation of Th2 development (Fig. 2).

3.3. Interaction of DCs with SCFAs

As it is known, an intestine contains approximately 97% of the commensals of human microbiota, and they exert the greatest influence on the entire organism [75]. In addition to the molecular patterns that make up the bacterial cell, bacteria produce unique metabolites. They could be called molecular patterns of bacterial metabolism. The presence of these metabolites and their concentration indicate the active life of bacteria of certain species in the intestine. Such metabolites are: SCFAs, SBAs, tryptophane metabolites (indole), vitamins, neurotransmitters and AI of bacteria.

SCFAs, such as acetate, butyrate, and propionate, are the end products of microbial fermentation of dietary fibers in the gut (ileum and colon) and represent 95% of the total SCFAs content in the intestine. Bacteria of different species could produce SCFAs using different biochemical pathways (Table 2) [76–79]. The molar ratio of acetate, propionate, and butyrate production in the healthy colon is approximately 60:25:15, respectively [28]. This ratio also varies depending on site of fermentation, diet, microbiota composition, and pathologies. Since these compounds are of low molecular weight, they are easily absorbed into the blood, through the portal vein they enter the liver, where part of them is utilized, the other part enters the circulation, where the molar ratio for acetate/propionate/butyrate is 90-55/35-5/10-4 respectively depending on portal, hepatic and peripheral origins [80]. Therefore, they realize their activity locally and systemically because they are distributed systemically through the blood to tissues.

SCFAs act on sensitive cells by three fundamentally different mechanisms. Firstly, they interact with the appropriate cell receptors and initiate signal cascades involved in cell proliferation and differentiation processes. Secondly, through the channels in the membrane, SCFAs can directly penetrate into the cell and affect cellular metabolic processes. Thirdly, butyrates and, to a lesser extent, propionates, upon direct penetration into the cell, participate in the inhibition of histone deacetylases (HDAC), thereby influencing the functioning of the cell genome [72,76].

SCFAs exert their effects through G-protein-coupled receptors (GPCRs). The major GPCRs are GPR43 (FFAR2), GPR41 (FFAR3), and GPR109A (HCAR2) for both murine and human immune cells [81–83]. Different SCFAs interact with FFAR receptors with a diverse affinity (FFAR2 – C2═C3 > C4 > C5═C1, FFAR3 – C3═C4═C5 > C2 > C1) [83]. After engaging these receptors, SCFAs induce certain signaling cascades. In addition, SCFAs can directly enter cells with the participation of transporters, for example, MCT1 (SLC16A1), MCT4 (SLC16A3), SMCT1 (SLC5A8), and SMCT2 (SLC5A12) [84] and affect certain biochemical events. For instance, butyrates, when entering the colonocytes, serve as a source of energy in the tricarboxylic acid cycle.

Furthermore, SCFAs have immunomodulatory effects [85,86]. Among SCFAs, butyrate has received particular attention because of its beneficial effects on cellular energy metabolism, immune function, and intestinal homeostasis [87]. Generally, SCFAs, like propionate and butyrate, decrease stimuli-induced expression of adhesion molecules, chemokine production by neutrophils, macrophages and endothelial cells. It consequently suppresses monocyte/macrophage and neutrophil recruitment to sites of inflammation. Butyrate-treated macrophages exhibited transcriptomic signatures that corroborate with an M2-like prohealing phenotype. Besides, butyrate quelled LPS-mediated catabolism and phagocytosis of macrophages and induced death of proinflammatory macrophages *in vitro* and *in vivo* [88]. It suggests an anti-inflammatory action of SCFAs. However, there are also evidences on support of pro-inflammatory action of SCFAs in some conditions [89,90].

SCFAs could directly influence the activity of T cells. For example, they promote the differentiation of T lymphocytes into effector regulatory T cells (Treg) via HDAC inhibition [91]. Butyrate and propionate directly influence gene expression in $CD8^+$ cytotoxic T lymphocytes (CTLs) and T cytotoxic 17 (Tc17) cells and enhance the activity of these cells [92]. Arpaia N et al. in experiments on mice models showed that butyrate induced Treg differentiation *in vitro* and *in vivo*. It was concluded that the effect of butyrate was both direct and DC-mediated [75].

SCFAs influence the physiological activity of human DCs that, as APCs, have the ability to shape the immune system's response. DCs express different receptors for SCFAs. Caudia Nastasi et al. (2015) investigated that human monocyte-derived DCs, like primary human CD1c+ and CD141+ DC, expressed GPR41 and GPR109A and had the ability to respond to SCFA through these receptors [28]. When human MDDCs were treated alternately with acetate, propionate, and butyrate after exposure to LPS, no marked changes in the expression of HLA-DR or CD86 molecules were detected. Whereas the LPS-induced expression of CD83 was significantly reduced by the exposure to both propionate and butyrate when compared to normally matured DCs. It was also shown that both propionate and butyrate reduced the LPS-induced IL12p40 and IL-6 production and corresponding gene expression. Analysis of the expression of cytokine genes in DCs showed that the general effect exerted by SCFA can be ranked as: acetate < propionate < butyrate. Of note, butyrate demonstrated a more profound effect on MDDCs [28]. This investigation also demonstrated that SCFAs decrease the gene expression and protein synthesis of proinflammatory chemokines. Acetate reduced the release of CCL3, butyrate decreased CCL4, CCL5 and CXCL9, −10, −11 and propionate decreased CCL3, CCL5 and CXCL9, −10, −11. These inflammatory chemokines regulate cell

Table 2
Bacteria – producers of SCFA [53,54,69].

SCFAs types	Bacteria - producers
Acetic acid	*Prevotella spp., Bifidobacterium spp., Bacteroides spp., Akkermansia muciniphila, Clostridium spp., Streptococcus spp., Ruminococcus spp., Blautia hydrogenotrophica*
Propionic acid	*Bacteroides spp., Megasphaera elsdenii, Veillonella spp., Coprococcus catus, Akkermansia muciniphila, Phascolarctobacterium succinatutens, Dialister spp., Roseburia inulinivorans, Blautia obeum, Eubacterium hallii*
Butyric acid	*Clostridium spp., Coprococcus comes, C. catus, C. eutactus, Faecalibacterium prausnitzii, Eubacterium hallii, E. rectale, Ruminococcus bromii, Anaerostipes spp., Roseburia spp., Subdoligranulum spp., Anaerobutyricum spp.*

traffic within secondary lymphoid tissues and could influence T cell development after antigen recognition. Authors also hypothesized that SCFAs could shape the naive T-cell polarization by decreasing the pro-inflammatory Th1 and Th17 phenotypes and therefore changing the balance towards anti-inflammatory populations such as Tregs. In addition, it was shown that the activity of butyrate and propionate is somewhat selective because these SCFAs affect primary LPS response genes like TNF-α family genes and CCL2, while other LPS response genes such as CD86, HLA-DR, IL-1A, IL-1B, were unaffected [67]. It was found in the murine BM-DCs model that treatment of these cells with butyrate also led to a decrease in *Tnf* gene expression previously induced by LPS [84].

Claudia Nastasi et al. (2017) [93] showed that butyrate and propionate influence the maturity state and functions of human MDDCs. A significant decrease in the expression of the co-stimulatory molecules CD83, CD80, and CD40 after butyrate treatment and a notable reduction in CD83 and CD80 expression after propionate have been detected in LPS stimulated MDDCs. They found that butyrate and propionate inhibit the production of IL-12 and IL-23 in the MDDCs. Then it was shown that these SCFAs reduce the activation of $CD8^+$ CTLs in T cell-DC co-cultures. It stressed a pivotal role of butyrate and propionate in modulating $CD8^+$ T cell activation via the inhibition of surface markers expression and cytokine secretion by DCs. These results revealed a novel mechanism whereby bacterial fermentation products as SCFAs may modulate $CD8^+$ T cell function. Possibly, this knowledge could be applied to anti-cancer immunotherapy strategies.

The results obtained by the group of Urribe-Herranz Mireia demonstrated that the APC function of DCs was inhibited by butyrate alone. It has been shown by decreased amount of IFN-γ–secreting cells after cultivation of naive mice T cells with BMDCs treated with butyrate relative to untreated control. Interestingly, propionate-treated DCs also exhibited a partial inhibition of antigen presentation when used alone but did not potentiate the inhibition induced by butyrate alone [94]. These data confirm the impact of SCFAs on DCs phenotype and inhibition of antigen presentation. The removal of butyrate-producing bacteria generally contributed to the effectiveness of radiation therapy through better processing and presentation of antigens by CD11c + DCs that resulted in effective secretion of IFN-γ and activity of $CD8^+$ effector T cells [94]. Obtained results suggest that response to antitumor therapies in mice is mediated by a complex interplay between microbes and immune system interactions.

Eleonora Ciarlo et al. [95] investigated the role of propionate in infectious process in mice. They showed in *in vitro* studies that mice BM-DCs were significantly inhibited by propionate to produce TNF and IL-12p40 in response to LPS, Pam3CSK4 (a lipopeptide that triggers cells through TLR1/TLR2), or *S. aureus* treatment. Besides, propionate slightly increased *E. coli*-induced IL-6 and IL-12p40 production by BM-DCs [95]. However, in a mouse *in vivo* model with endothexinemia induced by opportunistic microorganisms *S. aureus*, *Klebsiella pneumoniae*, and *Candida albicans*, it has been shown that pretreatment of animals with propionate (in food) had no impact on the final result – animal morbidity and mortality from induced infection [95].

Maria M. M. Kaisar et al. [96] proposed the complex mechanism of butyrate impact on human DCs. They also confirmed that butyrate and, to a lesser extent, propionate and acetate suppressed the LPS induced upregulation of costimulatory markers CD83, CD80, and CD40 and decreased the production of both IL-10 and IL-12 by hMDDCs. They also found that butyrate via engagement of surface receptor GPR109A and through the mechanism of deacytylation inhibition, induced the retinaldehyde dehydrogenase 1 (RALDH1) expression and activity in human DCs [96]. This results in retinoic acid production by DCs that polarize the immune response into the development of Treg cells. They also found that butyrate influences DCs' metabolism by means of lowering glycolysis and oxidative phosphorylation (OXPHOS) [96]. Thus, butyrate treatment induced tolerogenic phenotype in human DCs.

Wenbo Xiu et al. [97] showed another mechanism of SCFA impact on DCs. They found that butyrate induced the production of the epidermal growth factor (EGF) family member amfiregulin (AREG) by mice DCs. Recently, AREG has been characterized as a novel cytokine that contributes to Treg cell development [98].

This property of butyrates to promote the development of immune tolerance mechanisms, namely the promotion of high Treg content, can have negative consequences. Clélia Coutzac et al. [99] investigated that butyrate decreased the expression of CD80 and CD86 molecules on DCs treated with anti-CTLA-4 MKAT *in vitro*. In addition, in the *in vivo* system, the concentration of butyrate in the blood serum of mice was inversely correlated with the expression of CD80 and CD86 on DCs. Artificially increasing the butyrate content in the peripheral blood of mice impaired the effectiveness of CTLA-4 blockade therapy. Therefore, it was shown that butyrate inhibits DC maturation and disrupts the antitumor effect of CTLA-4 blockade in mice tumor model [99].

Kayting Yang et al. [100] showed that mice BM-DCs treated with sodium butyrate *in vitro* had decreased expression of INF-β at the gene and protein levels. Authors extrapolated these results to the situation *in vivo* and suspected that produced by microbiota butyrate could act systemically and decrease the efficacy of radiation antitumor therapy via suppression of the antitumor immunity. In *in vivo* model, they used vincomycin to eradicate some species of butyrate producing bacteria and decrease the concentration of butyrate in the circulation and tumor tissue of mice. It was associated with enhanced antitumor responses to ionizing radiation. In contrast, oral administration of Lachnospiraceae, a family of vancomycin-sensitive bacteria, in GF mice was associated with increased systemic and intratumoral butyric acid levels and impaired efficacy of ionizing radiation antitumor therapy. Finally, they concluded that butyrate might reduce the efficacy of ionizing radiation therapy on various cancers [100].

Through DCs activity, butyrates influence the humoral immune reactions in the gut. Junya Isobe et al. [101] showed that butyrate enhanced the production of TGF-β and all-trans retinoic acid by CD103 + CD11b + DCs *in vitro*. This effect was mediated by G-protein-coupled receptor 41 (GPR41/FFA3) and GPR109a/HCA2, and the inhibition of histone deacetylase activity. Produced by DCs cytokines are necessary for T-independent IgA production. This is important for maintaining the integrity and resistance of the mucous membrane to the penetration of bacteria.

The diet with a high content of digestive fibers, the substrate for butyrate-producing bacteria, is associated with changes in organism immune activity. An increased number of CD103+ DCs in mesenteric lymph nodes was found in mice fed a high fiber (HF) diet and increased butyrate content in the intestine. *In vitro* investigation of these cells showed they were more potent in converting naive T cells to FoxP3+ Treg lymphocytes. Therefore, HF diet feeding enhances the content and tolerogenic activity of CD103 + DCs, which is

dependent on the retinoic acid signaling pathway [102]. In another study, mouse BM-DCs treated with a filtered supernatant of *Clostridium butyricum* (a known colon butyrate producer) *in vitro* reduced the production of pro-inflammatory cytokines IL-1β and IL-6 [103].

Thus, SCFAs produced by some gut microbiota species systemically affect the maturation and physiological activity of human DCs. Among the three SCFA studied, butyrate and propionate exert the main immunomodulatory role directly influencing the gene expression profile in DCs and contributing to the tolerogenic phenotype of these cells. In different physiological situations, it could have diverse consequences and results. It is worth noting that butyrate could suppress the pro-inflammatory effect of LPS on DCs. These data open a new perspective on the SCFAs ability to shape the immune response through DCs, regulating leukocyte recruitment and polarization of specific immune reactions.

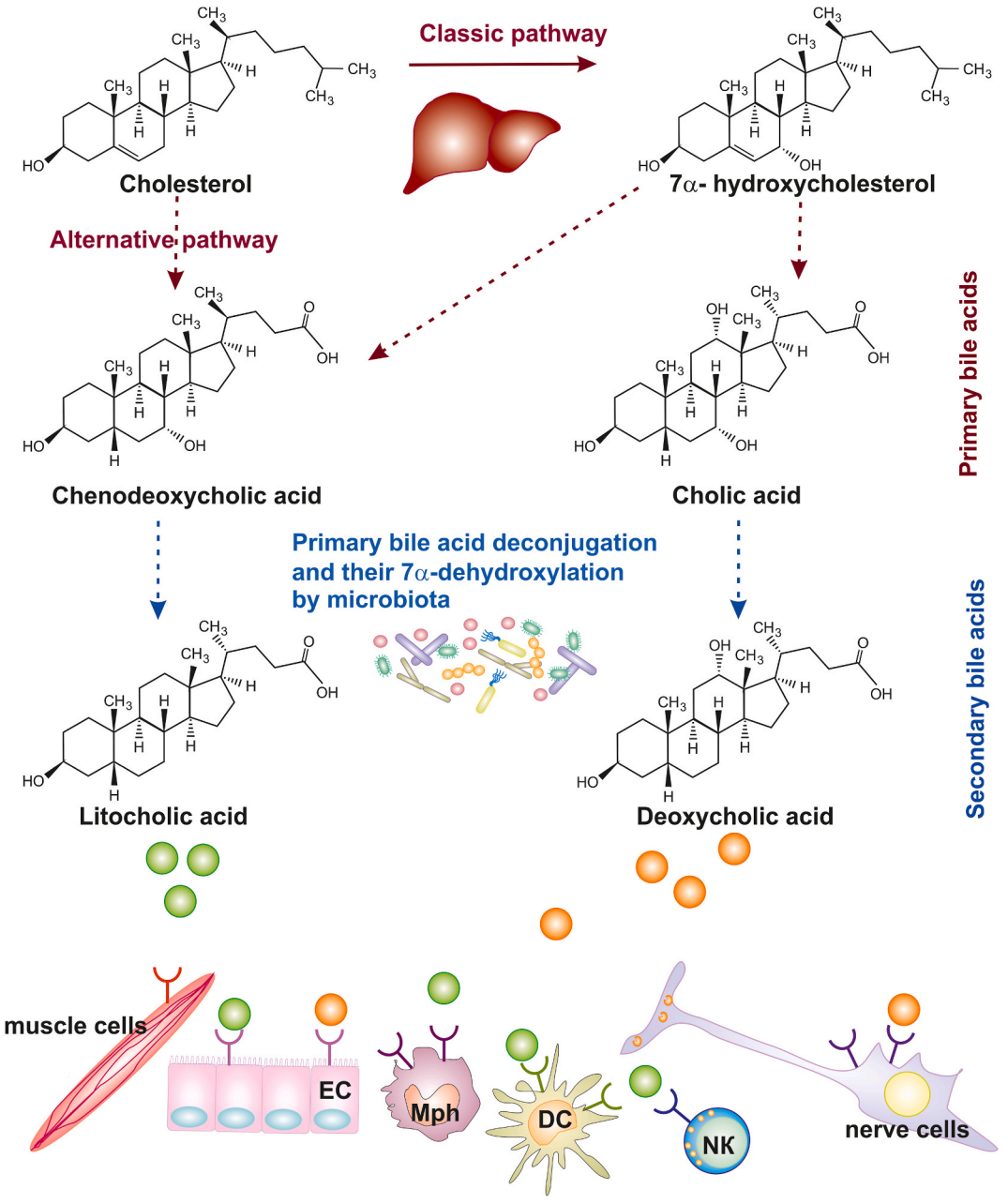

Fig. 3. Primary bile acids conversion by microbiota to secondary bile acids, bile acid metabolites, and their impact on DCs. EC – epithelial cells, Mph – macrophages, NK – natural killer cells.

3.4. The effect of secondary bile acids on DCs

Commensal human body bacteria are involved in the metabolic transformations of certain biologically active substances produced in the macroorganism, such as bile acids [104]. Primary bile acids are synthesized in the liver from cholesterol and are represented mainly by cholic acid (CA) and chenodeoxycholic acid (CDCA). Then, they are further conjugated with glycine or taurine and released through bile ducts into the duodenum. Approximately 95% of the primary bile acids are recycled. They are actively reabsorbed in the terminal parts of the ileum and returned to the liver through the portal vein. However, approximately 5% of bile acids are deconjugated and biotransformed into SBAs by commensal bacteria enzymes. Bacteria of the ileum (of the genera *Clostridium*, *Bifidobacterium*, *Enterococcus*, *Lactobacillus*, *Bacteroides*, as well as *Methanobrevibacter smithii*, *Methanosphera stadmanae*) produce bile acid hydrolases (Bile Salt Hydrolase, BSH), which deconjugate bile acids. Further, enzymes of other bacteria (*Clostridium* and *Eubacterium*) due to the process of 7α-dihydroxylation contribute to the formation of secondary bile acids: deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) [105] (Fig. 3). Further corresponding enzymes of human gut bacteria convert the secondary bile acid lithocholic acid into 3-oxolithocholic acid (3-oxoLCA) and abundant gut metabolite isolithocholic acid (isoLCA) [106].

Primary and secondary bile acids and their metabolites perform certain signaling functions, which are not completely known today. Bile acids interact with certain Bile Acid Receptors (BARs) as signaling molecules. The most studied examples of them are: nuclear FXR (Farnesoid X Receptor) and plasma membrane receptor GPBAR1 (G-Protein Bile Acid Receptor 1). Muscle cells, neurons, intestinal endothelium, and immune system cells express both receptors. Among immune cells monocytes, macrophages, DCs, natural killer cells (NK) and NK-T cells widely express these receptors [107,108]. Generally, it is known that signals through BAR on DCs, NK-T and macrophages lead to the development of such reactions, which are anti-inflammatory by their nature [109–111]. Recently, other receptors for bile acid metabolites have been characterized. For example, such metabolite of LCA as isoLCA acts on immune cells through blocking the function of the nuclear hormone receptor (NhR) RORγt [112] that results in the inhibition of Th17 function [106].

Studies of the effects of secondary bile acids and bile acid metabolites formed by commensal bacteria on DCs are rare. However, it has been investigated that secondary bile acids affect the state of maturity and functional activity of DCs, which was proven *in vitro* and *in vivo*. *In vitro* experiments showed that treatment of human MDDCs with secondary BAs (LCA and DCA) led to a decrease in IL-12p40 and TNF-α production by the cells [72]. However, the study's authors noted that this effect was insignificant. Jianping Hu et al. [29] also showed that LCA, DCA, and UDCA inhibited the secretion of several pro-inflammatory cytokines, including IL-12/p70, IL-1β, IL-23, IL-6, and TNF-α by mice BMDCs. However, DCA and LCA further slightly inhibited the expression of the surface markers CD40, CD86, CD80, and MHCII in mice BM-DCs. LCA in these experiments demonstrated the greatest effect. These findings suggest that LCA regulates the function of DCs via the signaling through Takeda G-protein coupled receptor 5 (TGR5). CD11c + DCs isolated from TGR5+/+ mice (with experimental autoimmune uveoretinitis) fed LCA diet significantly inhibited the differentiation of Th17 and Th1 cells and the secretion of IL-17 and IFN-γ respectively [29]. Therefore, the effect of secondary bile acids and bile acid metabolites formed as a result of microbiota activity on DCs is such that it enhances the anti-inflammatory functions of these cells. In other *in vivo* study it has been shown that bile acids produced by gut commensals suppress the severity of experimental autoimmune uveitis. Authors evidenced that this effect was mediated via a TGR5-induced inhibition of DCs activation [113].

3.5. Bacterial autoinducers and DCs

Bacteria living in natural econiches, including microbiotopes of the human body, have developed biochemical communication mechanisms over millions of years of evolution. They regulate the behavior of all communities of bacteria belonging to one or different species by means of synchronization of the expression of certain genes. This principle of bacterial intercellular communication was named quorum sensing (QS), as it depends on the number of bacteria in the population [114]. Under QS, there are regulation of various physiological activities, production of necessary metabolites and macromolecular substances and size of bacterial population [115]. The most studied areas of application of the QS principle are the formation of bacterial biofilms and the development of the infectious process [115,116].

The "language" of intercellular communication of bacteria is implemented by small signaling hormone-like molecules called AI. Gram-negative bacteria use acylated homoserine lactones (AHLs or HSLs) and diffusible signaling factors (DSFs) as autoinducers. Gram-positive bacteria are used as AI auto-inducing peptides (AIPs). For interspecies communication, bacteria mainly use autoinducer 2 (AI-2) and indole [117,118]. The human body's cells also "understand" the chemical language of bacteria. The cells of various tissues, including the cells of the immune system, respond to interaction with autoinducers, which is the phenomenon of "inter-kingdom signaling" [119,120]. The molecular mechanisms of AI action on eukaryotic cells are still being studied. For example, it is known that AHL is chemically analogous to many lipid-based hormones such as the eicosanoid family of lipidic and steroid hormones involved in hundreds of biological functions in eukaryotes, could enter the host cell, bind to intracellular receptors, and regulate gene transcription [121].

Although studies of the direct influence of autoinducers on the immune cells functions are quite limited, it has been shown that bacterial autoinducers exhibit immune-modulating properties [119,122]. The results of *in vitro* and *in vivo* experiments are contradictory. Different AIs showed both anti-inflammatory and pro-inflammatory activity. For example, AI-2 produced by nonpathogenic *E. coli* revealed a significant increase of IL-8 secretion by epithelial intestinal cells in 6 and 12 h, followed by a significant down-regulation at 24 h. It means that AI-2 as a single signal molecule has pro-inflammatory activity in the early stages after treatment of epithelial cells [95]. Epithelial cells contribute to the development of innate immune response and are early producers of chemotactic factor for neutrophils IL-8 [123]. In another investigation, AI-2 promotes the production of serum amyloid protein-1 (SAA1) and SAA2

by the host, which increased Th17 cell production in mice [124]. Produced by *F. nucleatum* AI-2 induced inflammatory responses and activated multiple signaling pathways in macrophages [35]. Jiao Wu et al. [125] showed that *F. nucleatum* AI-2 enhanced macrophage mobility and M1 polarization, possibly through TNFSF9/TRAF1/p-AKT/IL-1β signaling. However, in some *in vivo* experiments, the anti-inflammatory activity of AI-2 was detected. Exogenous AI-2 partially reverses microbiota disorder and decreases inflammation in a necrotizing enterocolitis in mouse model [126]. Of note, in this experimental model, the effect of autoinducers was not only direct but also mediated by changes in the composition of the microbiota. In this study, AI-2-induced reduction of inflammation in the intestines of mice was associated with a partial restoration of the microbiota composition [126].

Yifat Glucksam-Galnoy et al. [127] showed that bacterial autoinducer N-3-oxo-dodecanoyl-L-homoserine lactone (3-oxo-C12-HSL), known to be produced by *Pseudomonas aeruginosa*, demonstrated *in vitro* the ability to down-regulate production of the key pro-inflammatory cytokine tumor necrosis factor α (TNFα) that positively correlated with increased expression of IL-10 in LPS stimulated mice macrophages. In other investigation, this AI inhibited human T-cell proliferation and IL-2 secretion [128].

Studies on the impact of AI directly on DCs are very scarce. In some investigations [30], the impact of AIs on DCs was shown. The autoinducer N-octanoyl-L-Homoserinehomoserine lactone (C8-HSL) used as a major inter- and intraspecies communicator, mainly for Gram-negative bacteria, was evidenced to have immunogenic properties. In *in vitro* investigation C8-HSL increased autophagy and NO• release in DCs. This autoinducer in microparticle formulation displayed adjuvant potential and was even proposed to be used as a component of both antibacterial and antiviral vaccines.

Two autoinducers produced by *P. aeruginosa* N-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) and the Pseudomonas quinolone signal (PQS) decrease the production of interleukin-12 (IL-12) by *Escherichia coli* LPS-stimulated mouse BM-DCs without altering their IL-10 release. Moreover, BM-DCs exposed to PQS and 3-oxo-C12-HSL during antigen stimulation showed a decreased ability to induce T-cell proliferation *in vitro*. These results suggested that both *P. aeruginosa* autoinducers 3-oxo-C12-HSL and PQS could change the maturation pattern of stimulated DCs away from a pro-inflammatory T-helper type 1 response, thereby decreasing the antibacterial activity of the adaptive immune defense. Thus, 3-oxo-C12-HSL and PQS seemed to possess dual activities in the infection process: as inducers of bacterial virulence factors, as well as immune-modulators that facilitate pathogen to evade host immune response [129].

Pisake Boontham et al. [130] showed that 3-oxo-C12-HSL inhibited human MDDCs proliferation and decreased LPS-induced CD86 expression. This autoinducer also induced apoptosis in DCs through cytochrome *c* release and caspase-3 activation pathway. 3-oxo-C12-HSL treated DCs induced production of IL-4 and IL-10 in allogenic lymphocytes in mixed lymphocyte-dendritic cell reaction. Alternatively, IL-6, TNF-α, and IFN-γ production decreased.

Thus, autoinducers of bacteria may have many mechanisms of action. Besides the direct regulation of the collective behavior of bacteria, these substances may be important for interkingdom communication. They also demonstrate immunomodulatory activity. Different autoinducers have direct mechanism of action on the cells of the immune system and can realize both pro-inflammatory and anti-inflammatory effects. For example, an inhibition of inflammation development due to the action of AI *P. aeruginosa* 3-oxo-C12-HSL can be considered as a variant of immune response evoidance by opportunistic bacteria [129].

It is also necessary to take into account the indirect effects of AIs that are realized by modulation of composition and metabolical activity of microbiota. As a result, the interaction of the microbiota with the immune system changes. Some authors suggest using AIs (AI-2 and AHL) as possible targets for treating inflammatory bowel diseases [122,126].

4. DCs simultaneously receive complex signals from microbiota

Of course, in the human organism, in contrast to *in vitro* experiments, DCs simultaneously receive and integrate a number of different signals from commensal bacteria and the macroorganism's own cells and cytokines. To accomplish this, DCs have a wide range of appropriate receptors for recognizing various bacterial substances. To recognize MAMPs, DCs use PRR receptors; to recognize bacterial metabolites as SCFAs and BAs, DCs use FFARs and BARs, respectively.

The complex effect of bacterial substances on DCs was shown in experiments where combinations of LPS and PGN, whole living and inactivated bacterial cells, bacterial extracellular vesicles, as well as the secrets of bacterial cultures were used. Similar studies can be carried out *in vitro* when using special insert systems for cultivation of eukaryotic and bacterial cells simultaneously. In such studies, it was shown that combinations of different bacterial substances on DCs could modulate the activity of APCs in a special way, which depends on the biochemical properties of these substances produced by bacteria of different species.

For example, if human MDDCs were treated with PGN of *L. rhamnonus* after treatment with *E. coli* LPS, then a decrease in the expression of HLA-DR, CD80, and CD83 markers was observed (after treatment with pure PGN expression of these markers on MDDCs was unchanged). Also, an increase in secretion cytokines TNF-α and IL-10 (pure PGN induced only TNF-α secretion) was detected [49]. It was simultaneously studied the effect of cell wall preparations on the functional and phenotypic maturity of DCs. In comparison with purified PGN, the preparation of cell walls did not affect the expression level of CD80 but increased the expression of HLA-DR, CD86, and CD83. The preparation of cell walls also stimulated the secretion of pro-inflammatory cytokines TNF-α and IL-8 [57].

In one of the studies, secretomes of commensal skin bacteria were used to activate human DCs and polarize allogeneic $CD4^+$ T cells [131]. Secretomes were the filtrate of culture medium RPMI 1640, in which bacteria that were in the stationary phase of growth were grown overnight. Therefore, in essence, secretomes are a composition of metabolites and components of the cell wall of bacteria that exfoliate during the stationary phase of growth [48], as well as exotoxins of staphylococci. It was shown that the secretomes of *S. aureus* and *S. epidermidis* had oppositely directed effects on DC phenotype and functions. The former promoted the maturation of DCs that highly expressed DCs maturity markers CD86, CD83, HLA-DR and produced IFN-γ, but later induced the development of DCs that expressed lower levels of CD86, CD83, and HLA-DR and secreted IL-10 [131]. *S. aureus* secretomes stimulated MDDCs induced

differentiation of Th1, as *S. epidermidis* secretomes stimulated MDDCs induced Treg differentiation. It is important that when moDC were pulsed with mixtures of *S. epidermidis* secretomes and *S. aureus* secretomes at various ratios and then co-cultured with allogeneic $CD4^+$ T cells opposing effects were obtained. The addition of increasing amounts of *S. epidermidis* secretomes to a given amount of *S. aureus* secretomes significantly decreased T cell proliferation. It suggests that commensals such as *S. epidermidis* may play a prominent role in controlling the inflammatory effects of cutaneous *S. aureus* at the level of DCs. Therefore, bacterial secreted substances belonging to bacteria of different species have diverse effects on the functional activity of DCs and the balance of received signals determines the "fate" of the immune response in general.

Natalia Diaz-Garrido et al. [132] showed that human MDDCs were treated with bacterial exosomes (BEV) obtained from the probiotic strain *Escherichia coli* EcN and commensal *Escherichia coli* strain isolated from the fecal samples of a healthy human adult ECOR12. DCs stimulated with BEVs from probiotic EcN secreted higher levels of Th1-driver cytokines INF-γ and IL-12 than DCs stimulated with BEVs from the commensal ECOR12. Besides, the highest level of the Treg-polarizing cytokine TGF-β was detected after the treatment with ECOR12 BEVs. Probiotic EcN BEVs also induced TGF-β secretion by DCs. BEVs from both EcN and ECOR12 activated secretion of Th2 and Th17-polarizing cytokines (IL-4 and IL-6) and IL-10 without significant differences between strains. Thus, significant differences in the Th1 and Treg polarizing cytokines were observed between DCs stimulated with BEVs from probiotic EcN or normal commensal ECOR12. It means that strains of commensal bacteria could be highly adapted for growth in host organism without the induction of inflammation.

Studies of the complex effect of bacterial substances on the immune system cells *in vivo* are of great interest [133,134]. It is rather problematic to study such an effect on DCs, as they are present in small quantities in organs and tissues. A similar study was conducted using alveolar macrophages. In this study, using human and mouse biological material, it was shown that LPS and SCFAs produced by intestinal microbiota are present in lung tissue. Propionate was found to affect the metabolic reprogramming of LPS-stimulated alveolar macrophages in a dose-dependent manner [133]. The treatment of alveolar macrophages with LPS led to an increase in glycolysis in them. Further, the treatment of such LPS-induced alveolar macrophages with propionate influenced the switch of metabolism from glycolysis to oxidative phosphorylation. Using germ free mice it has been shown that both LPS and propionate in lung tissue originate from the gut microbiota. These bacterial substances are components of the microenvironment and create a background for development of immune reactions in the lung tissue. The proinflammatory activity of alveolar macrophages was dependent on exposure to LPS and could be reprogrammed by propionate in a dose-dependent manner [133]. It can be speculated that DCs are also subject to similar impacts. In another study, the authors investigated the mechanism of "instructing" cDCs in a steady state by commensal microbiota and pDCs in mice [134]. This phenomenon was realized by the continuous process of pDC-produced IFN-I signaling on cDCs tissues. It is still unknown which bacterial substances were involved in this mechanism. Future investigations in this field are needed to understand the nature of this phenomenon and the possible application of this knowledge to enhance the efficacy of DC-based antitumor immunotherapy.

Summarizing all of the above, we can conclude that, in general, bacterial substances can be divided into those that indicate the presence of bacteria, such as PGN, LPS, and bacterial DNA, and those that provide information about the vital activity of bacteria, that is, they are bacterial metabolites: SCFAs, SBAs, and AIs. Cells of the immune system, receiving various signals from commensal bacteria, have to integrate them and initiate certain immune response mechanisms. DCs has the widest range of receptors for recognition of various bacterial substances. It appears that the immune system implements an immune response by integrating a variety of biochemical signals from commensal bacteria of many species.

Thus, we proposed simplified model of bacterial substances impact on DCs. The involvement of PRR receptors (signal 1) provides information about the presence of a bacterial cell as such. The interaction of LPS and some bacterial species PGN with the corresponding PRR, TLR4, and TLR2 leads to the development of pro-inflammatory immune reactions. However, living bacteria in the human body produce unique metabolites characteristic only for them. They could be called Microoganism Metabolism Associated Molecular Patterns, or MMAMPs. These bacterial metabolites, such as SCFAs and sBAs, are also recognized by the corresponding receptors as FFARs and BARs, respectively. Therefore, the activation of these receptors (signal 2) indicates that the bacteria are alive

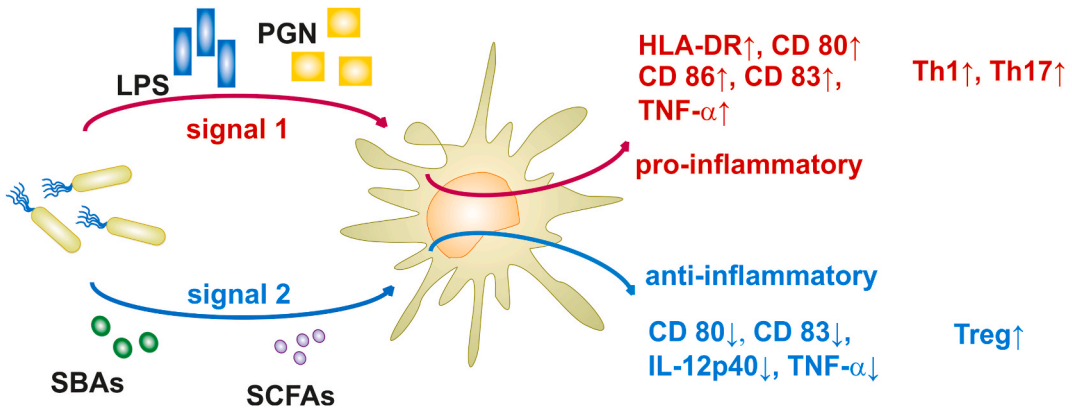

Fig. 4. Proposed simplified model of microbial signals impact on DCs.

and actively metabolizing. The effect of such commensal bacteria metabolites as SCFAs and sBAs on the immune system is mostly anti-inflammatory. Thus, the pro-inflammatory effect of the components of bacterial walls is partially compensated by the anti-inflammatory effect of the metabolites of commensal bacteria. The balance of signals determines the direction of the immune response (Fig. 4).

Therefore, the immune system and its sentinel cells DCs, due to the great variety of receptors and signaling cascades simultaneously integrate a whole series of signals and generate the most adequate to the antigenic and tissue situation response.

5. Conclusion

Physiological functions of DCs in any organs and tissues are influenced by the local tissue microenvironment. Today, we know that one of the important factors of this environment are bacterial substances produced by commensal bacteria.

The influence of live commensal bacteria on DCs function and tumor growth at the level of the whole organism has been discussed in one of the studies published in Science in 2015. It has been shown in the C57BL mouse model with B16 melanoma that the increased content of bacteria of genus *Bifidobacterium* in the intestinal microbiota was associated with a less aggressive course of the tumor process [135]. The more in-depth study proved that the basis of the more effective functioning of the immune system was the increased antitumor activity of DCs. DCs of mice with the high bifidobacteria content in the intestines expressed more MHC II and required less antigen for its effective presentation and activation of $CD8^+$ cytotoxic T lymphocytes. In addition, tumor-specific $CD8^+$ CTL were present in larger numbers in tumor-draining lymph nodes and produced markedly greater IFN-γ. In mice with a reduced content of bifidobacteria in the intestines, the effectiveness of antitumor immunity could be partially increased by oral administration of live (but not heat inactivated) bifidobacteria. At the same time, no spread of bacteria from the intestine to the microenvironment of the tumor, spleen or mesenteric lymph nodes was detected. One of the possible explanations for this phenomenon may be the systemic influence of living bacterial substances, for example, metabolites, on DCs. An indirect effect on the immune system of bacteria of other species cannot be excluded either. After all, the introduction of bacteria of the genus *Bifidobacterium* led to a change in the entire composition of bacteria in the intestine with a decrease in the representation of bacteria of other genera, for example, the genus *Clostridia*. This study also proved the positive effect of Bifidobacteria on the effectiveness of anti-PD-L1 immunotherapy [135].

Bacterial substances can be components of both the bacterial cell and bacterial metabolites. All these structures have an effect on various organs and systems of the macroorganism – first of all, the immune system. As the results of many studies show, different types of bacterial products can demonstrate opposite effects on the immune response. At the same time, such components of the bacterial cell wall as PGN and LPS mostly induce the development of pro-inflammatory reactions, while a number of bacterial metabolites – propionates, butyrates, secondary bile acids – demonstrate an anti-inflammatory effect [136]. It seems that in the human organism this balance of chemical signals from commensal bacteria greatly influences DCs functioning. Due to the action of various substances over millions of years of evolution, commensal bacteria have adapted to survive in the human macroorganism and manipulate its immune system.

The use of purified preparations of bacterial substances allows full control over the experimental conditions and can be useful for the development of vaccine preparations for general use. It is clear that in a living organism, the biochemical environment is much more complicated. Various bacterial substances belonging to bacteria of different species act simultaneously on DCs. Therefore, immune reactions to representatives of the microbiota are very ambiguous and depend on the type of bacteria, their localization in the body and metabolic activity, as well as genetically determined features of each individual's immune system. Thus, future studies of the effect on DCs of low-molecular and high-molecular substances produced by commensal bacteria in a mono-regimen or in a complex form (BEV, secretomes, whole bacterial cells) are very perspective. Studying these natural mechanisms of bacterial impact on the immune system and especially DCs allows us to better understand how to develop modern approaches to immunomodulation and immunotherapy for various human pathologies.

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CRediT authorship contribution statement

Yuliia Shvets: Writing – original draft, Supervision, Conceptualization. **Natalia Khranovska:** Validation, Investigation. **Natalia Senchylo:** Investigation. **Danylo Ostapchenko:** Validation. **Iryna Tymoshenko:** Validation. **Svitlana Onysenko:** Validation, Investigation. **Nazarii Kobyliak:** Writing – review & editing, Supervision. **Tetyana Falalyeyeva:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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