

Review

Metabolic crosstalk between intestinal microbiota and dendritic cells: from homeostasis to inflammation

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Abstract

The intestinal microbiota plays critical roles in regulating immunity and inflammation through intricate interactions between microbial metabolites and diverse immune cells. Dendritic cells (DCs), the most potent professional antigen-presenting cells, are essential for sensing the complicated microbiota environment and subsequently initiating and regulating adaptive immune responses. While the commensal microbiota typically mediates DC-triggered immune tolerance and thus the maintenance of intestinal homeostasis, epithelial injury or pathogenic infection generally drives the proinflammatory function of DCs, contributing to harmful inflammation and intestinal disorders. Various microbiota metabolites (such as short-chain fatty acids, bile acids, and tryptophan derivatives) play critical roles in modulating the developmental and functional diversity of DCs through metabolic, epigenetic, or signaling reprogramming. In this review, we discuss the metabolic crosstalk between the intestinal microbiota and DCs and its pivotal function in orchestrating the balance between intestinal homeostasis and pathogenic inflammation. We also discuss future directions to better elucidate the microbiota-DC dialog in intestinal immunity and develop therapeutic approaches for manipulating the microbiota-DC axis against inflammatory disorders.

Key words dendritic cells, intestinal microbiota, metabolites, inflammation

Introduction

The gut microbiota ecosystem, which consists of bacteria, viruses, and fungi, plays a pivotal role in human health and disease by dynamically interacting with the host immune system [1]. While proper regulation of microbiota-immune crosstalk is crucial for maintaining intestinal homeostasis, its dysregulation is closely implicated in various immune-mediated intestinal disorders, such as inflammatory bowel disease (IBD), infections, and tumors [2]. DCs are the master antigen-presenting cells that bridge innate and adaptive immunity. DCs are particularly capable of sensing and presenting microbial antigenic signals to the adaptive immune system, contributing to either tolerance to commensals and dietary antigens or immune defense against pathogens. Importantly, intestinal DCs display significant developmental and functional plasticity to cope with complicated intestinal environments [3–5]. Elucidating the molecular crosstalk between the microbiota and DCs is therefore critical for an in-depth understanding of how the host-immunity-microbiota network controls both intestinal homeostasis and immunological pathogenesis.

Immune-metabolism crosstalk has emerged as an essential mechanism linking the microbiota system to health and disease. Microbial metabolites are derived from multiple sources, such as dietary components, de novo synthesis, and metabolic switching, and are critical in modulating the function and metabolism of DCs in multiple physiological and pathological processes [6]. Various metabolites, such as short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives, are derived from the intestinal microbial system. These metabolites modulate the development, phenotype, and function of DCs through various mechanisms, such as intracellular signaling modulation, epigenetic reprogramming, and metabolic remodeling, thereby establishing a balanced response of the intestinal immune system. Importantly, intestinal dysbiosis, which is triggered by factors such as gastrointestinal infections, inappropriate diets and stressful psychological events, can lead to metabolic perturbations and aberrant activation of DCs, even causing inflammatory and neoplastic disorders [7,8]. Targeting microbiota-DC crosstalk through metabolic intervention strategies offers a promising direction for shifting harmful intestinal inflam-

mation to homeostatic tolerance. In this review, we discuss the current understanding of how microbiota-derived signals metabolically modulate the fate and function of DCs in intestinal health and disease pathogenesis.

Microbiota-Dendritic Cell Dialogue in Intestinal immunity

DCs, the most potent antigen-presenting cells, serve as critical sentinels at the interface between innate and adaptive immunity. DCs are widely distributed in distinct organs and tissues and actively reprogram the tissue immune ecosystem via complicated cellular and molecular interactions. Emerging evidence reveals that intestinal DCs orchestrate intestinal homeostasis and inflammation via mutual interactions with the gut microbial ecosystem.

cDC diversity in distinct tissues

The DC population exhibits considerable developmental, phenotypic and functional heterogeneity in health and disease. Several DC subsets have been identified, such as conventional DCs (cDCs),

plasmacytoid DCs (pDCs), monocyte-derived DCs (moDCs), and the recently characterized mature DCs enriched in immunoregulatory molecules (mregDCs), each with characteristic phenotypes, developmental pathways, metabolic and epigenetic signatures, and multifaceted roles in immune tolerance, defense, surveillance and homeostasis [9–11] (Figure 1). Among these, cDCs serve as the major DC subset within the intestinal microenvironment, where they dynamically interact with local immune and nonimmune cells to initiate and fine-tune antigen-specific immune responses and mucosal immunity [12].

cDCs are characterized by high expression of CD11c, a major histocompatibility complex class II (MHC II) molecule, and are developmentally dependent on the transcription factors *ZBTB46* and *Flt3* for their fate determination [13]. cDCs can be further classified into two major subsets: type 1 conventional DCs (cDC1s) and type 2 conventional DCs (cDC2s), each with distinct surface markers and functional specializations. The cDC1 subset generally expresses *CD8α* and *XCR1* and depends on transcription factors such as interferon regulatory factor 8 (*IRF8*), basic leucine zipper

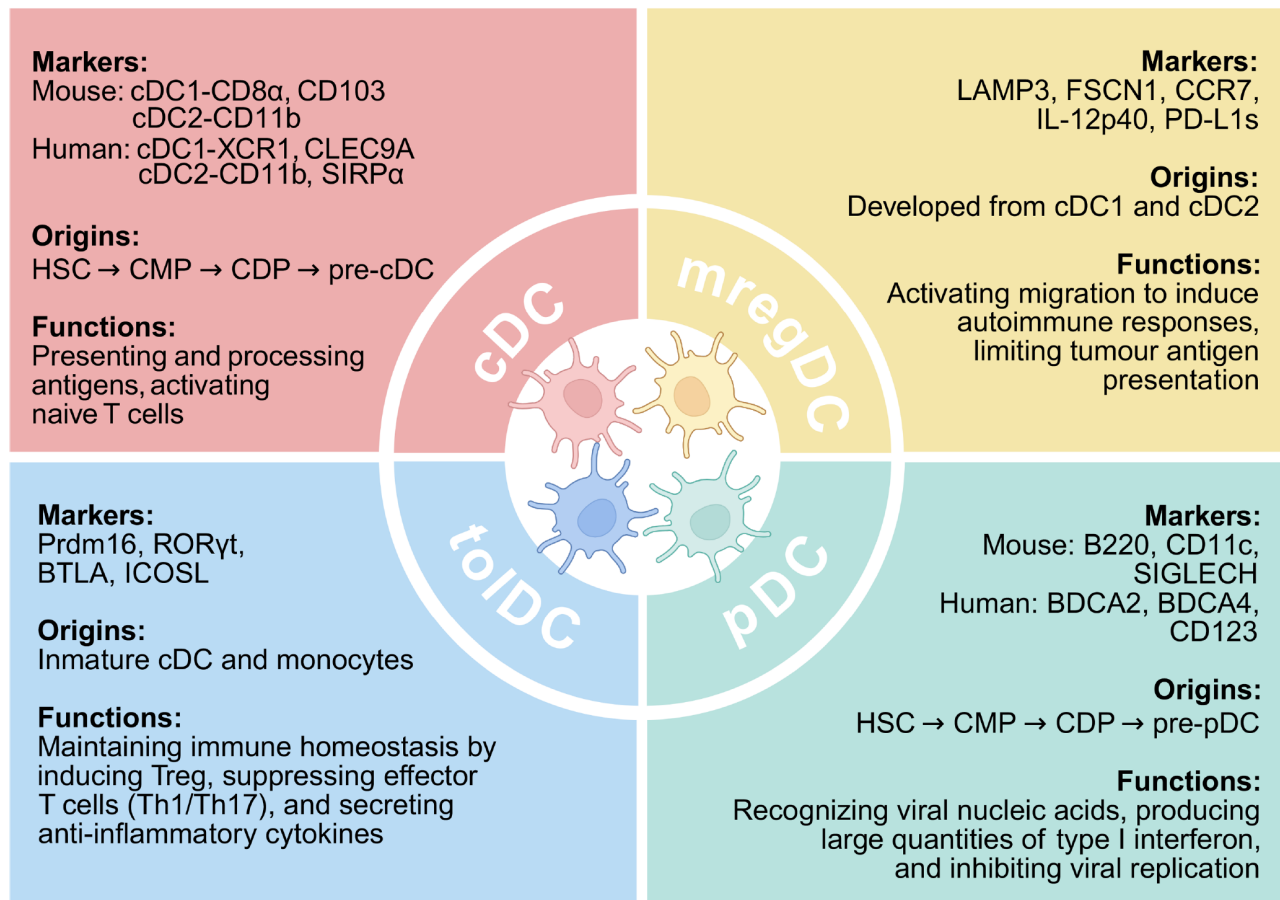


Figure 1. Characteristics and functions of major dendritic cell subsets This diagram illustrates four major dendritic cell populations: cDCs, mregDCs, pDCs, and toIDCs. cDCs can be further subdivided into cDC1 and cDC2 subsets, both of which are defined by specific surface markers in both mice and humans. They originate from common dendritic cell progenitor cells (precDCs) and are involved primarily in antigen presentation and T-cell activation. mregDCs develop from cDC1s and cDC2s, express *LAMP3* and *CCR7*, and function in activating migration to induce autoimmune responses while limiting tumor antigen presentation. pDCs arise from precDCs, are characterized by specific markers, including *BDCA2* and *CD123*, and specialize in recognizing viral nucleic acids and producing type I interferons to inhibit viral replication. toIDCs develop from immature cDCs or monocytes, express markers such as *Prdm16* and *RORγt*, and function in maintaining immune homeostasis by inducing regulatory T cells and secreting anti-inflammatory cytokines. cDCs, classical dendritic cells; toIDCs, tolerogenic dendritic cells; pDCs, plasmacytoid dendritic cells; mregDCs; migratory dendritic cells; Tregs, regulatory T cells; HSCs, hematopoietic stem cells; CMPs, common myeloid progenitors; CDPs, common dendritic cell progenitors.

transcription factor ATF-like 3 (*BATF3*), and zinc finger protein 366 (*ZFP366*) for its development. The cDC2 subset expresses relatively few specific surface markers, such as *SIRP α* , *CD11b*, macrophage galactose-type C-type lectin 2 (*MGL2/CD301b*), and C-type lectin domain family 12 member A (*Clec12a*). Functionally, cDC1s are potent in cross-presenting antigens to activate cytotoxic CD8⁺ T cells in response to tumor and viral infection, whereas cDC2s preferentially drive Th2 or Th17 cell activation in response to extracellular pathogen infection.

Notably, DCs are widely distributed in and frequently trafficked across distinct organs and tissues. The chemokine system and metabolic signals play potent roles in organizing the *in vivo* migration of DCs, which are essential for the rapid initiation of immune defense at infectious lesions while preventing harmful inflammation [14,15]. In addition, the identity and functional specialization of cDC subsets are spatiotemporally shaped by tissue-specific microenvironments, as exemplified by the unique tissue-specific cDC subclusters recently identified, such as Sirp α ⁺CD301b⁺ cDC2s in the thymus [16], CCR7⁺ migratory cDCs in lupus-lesional skin [17], and CXCL9-producing BATF3⁺ DCs in tumors [18]. The differential expression of CD103, CD11b and CX3CR1 divides intestinal DCs into distinct subclusters with distinct developmental origins and functional properties [19,20]. Such tissue-specific DC regulation emphasizes the importance of identifying new DC subsets in specific intestinal regions, new pathways of DC trafficking in and out of intestinal areas, and new mechanisms of microbiota-DC interactions in the orchestration of host immunity and inflammation.

Intestinal cDCs in homeostasis and inflammation

Under homeostatic conditions, intestinal DCs are regulated primarily by apoptotic cells, nonpathogenic antigens, or tolerogenic tissue environments and thereby function as tolerogenic DCs (tolDCs) [21]. Recent research has revealed that ROR γ t⁺ tolDCs are the key tolerogenic antigen-presenting cells required for intestinal tolerance, the development and function of which depend upon the expression of the transcription factors *Prdm16* and *ROR γ t*, as well as a unique *Rorc(t)* cis-regulatory element [22]. TolDCs produce inhibitory mediators such as transforming growth factor β (TGF- β) and IL-10 and express coinhibitory molecules such as PD-L1 and PD-L2, which jointly inhibit the functions of effector T cells (such as Th1, Th17, and Tfh cells), induce T cell apoptosis and exhaustion, and promote Foxp3⁺ Treg generation [23,24] (Figure 2). Transfection of FasL plasmids into primary DCs from the peritoneum of IBD model rats significantly reduces intestinal tissue damage and diminishes the infiltration of T cells, neutrophils, and proinflammatory macrophages in the colon, highlighting tolDCs as a novel therapeutic strategy for IBD [25].

On the other hand, epithelial damage, bacterial disturbance, or nutritional dysregulation trigger aberrant activation of mature DCs (mDCs) and subsequent adaptive immune responses, causing intestinal inflammation. While IRF4-dependent CD103⁺CD11b⁺ DCs favor the induction of intestinal Th17 cells in mesenteric lymph nodes (MLNs) [26,27], IRF8-dependent DCs control the differentiation of intestinal Th1 cells and host immune responses to *Trichuris muris* infection [28]. Thus, intestinal DCs dynamically maintain intestinal tolerance through Treg induction under homeostasis while driving aberrant adaptive immunity and inflammatory responses under inflammation.

cDCs widely exist in organized lymphoid tissues in the intestinal system, such as the lymphoid follicles (ILFs), lamina propria (LP), Peyer's patches (PPs), and MLNs [29]. Notably, the compartmentalization of the intestinal microenvironment plays important roles in shaping the functional plasticity of DCs. For example, proximal intestine-draining lymph nodes preferentially generate tolerogenic responses, whereas distal nodes promote inflammatory T cell responses. Migratory DC signatures and CD4⁺ T cell polarization are associated with differential immune properties in proximal versus distal lymph nodes [30,31]. Upon *Yersinia pseudotuberculosis* infection, however, migratory DCs improperly traffic toward the adipose compartment due to lymphatic leakage. This mislocalization of migratory DCs causes sustained inflammation post infection, as well as persistent impairment of canonical mucosal immune tolerance and protection [32]. In addition, DCs from gut-associated lymphoid tissues (GALTs) are able to induce IgA secretion by B cells in a manner dependent on DC-derived retinoic acid (RA) and cytokines such as IL-6 and IL-5 [33]. DCs located in the subepithelial dome (SED) of PPs are also able to induce IgA production by B cells via integrin α v β 8-mediated TGF- β activation [34]. Such compartmentalization of DC-mediated tolerance versus inflammation explains how the mucosal immune system maintains simultaneous tolerance to dietary antigens and protective defenses against harmful pathogens.

Microbiota control of intestinal cDC immunity

The coevolution of commensal microorganisms and the immune system has contributed to the dynamic balance between tolerance and immunity [35–37]. In healthy adults, the microbiota is dominated by *anaerobic Bacteroidetes* and *Firmicutes*, with relatively low levels of *Proteobacteria* and *Actinobacteria* [38,39]. These microbial components have various effects on modulating the host immune system [40–43]. For example, beneficial bacteria (e.g., *Bifidobacterium* and *Lactobacillus*) produce vitamins and metabolize nutrients for beneficial tolerance; opportunistic pathogens (e.g., *Escherichia* and *Enterococcus*) mediate harmful inflammation during dysbiosis; and pathogenic bacteria (e.g., *Salmonella*) invade the epithelial barrier and cause inflammatory responses [44–47]. The composition and metabolism of the microbiota continuously change under distinct biological and pathological conditions and thereby play highly flexible and widespread roles in modulating regional immunity and systemic homeostasis.

Intestinal DCs play central roles in sensing microbial signals and regulating immune responses. DCs can not only directly capture pathogens that actively invade the epithelium but also actively extend dendrites into the intestinal lumen to sample bacterial antigens for subsequent presentation in the MLNs [48]. The intestinal microbiota-derived pathogen-associated molecular patterns (PAMPs) can stimulate pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), which are expressed on the surface of intestinal epithelial cells (IECs) and DCs. This ligand-receptor interaction initiates complicated intracellular signaling cascades, leading to the release of thymic stromal lymphopoietin (TSLP) and TGF- β , which shift DCs toward a tolerogenic phenotype [49]. Gut microbes and IL-23 jointly upregulate CTLA-4 expression on the surface of Group 3 innate lymphoid cells (ILC3s), which subsequently downregulates CD80/CD86 while increasing PD-L1 expression on myeloid cells and consequently supports Treg and restricts effector T-cell responses [50]. Additionally, microbial

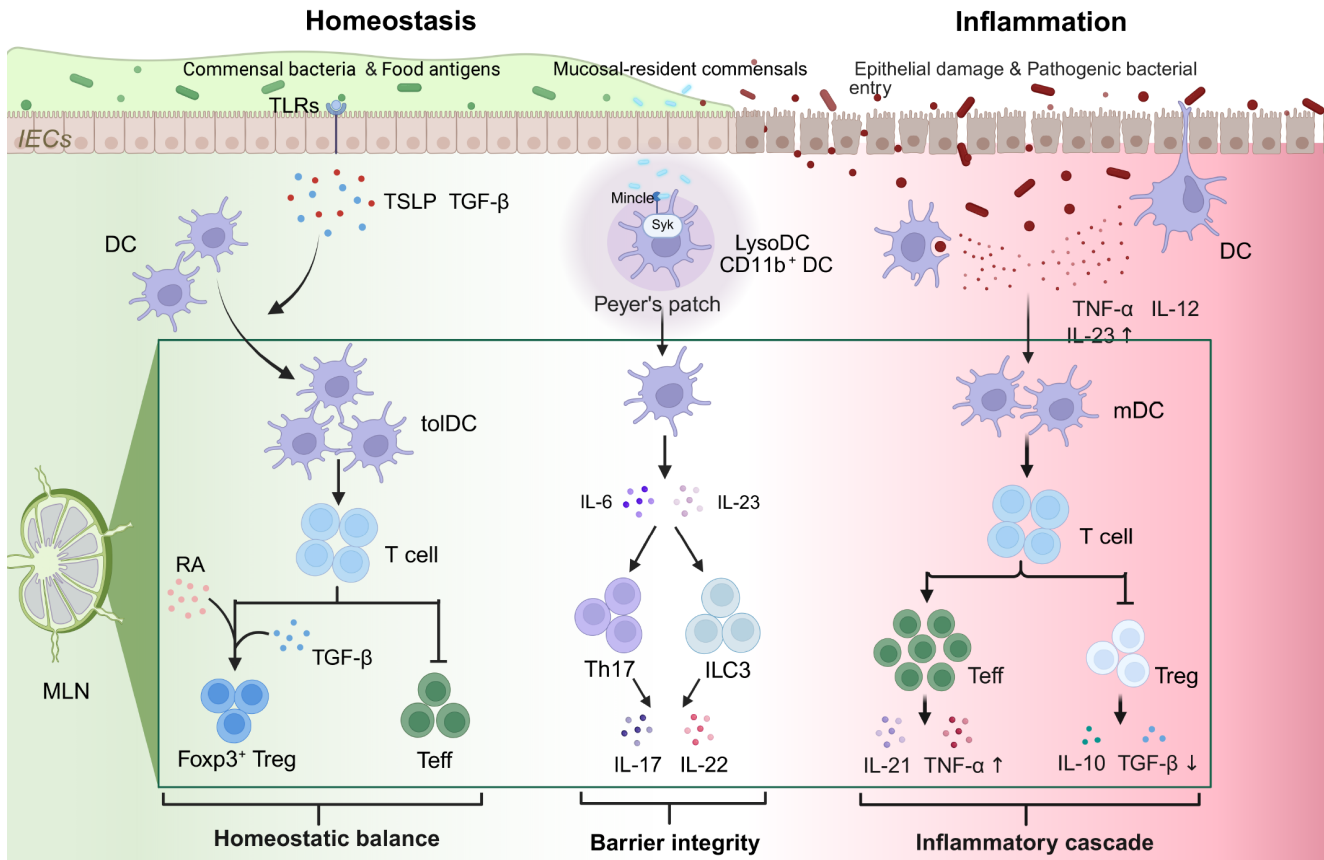


Figure 2. Microbiota-dendritic cell interplay in intestinal immunity The intestinal microbiota interacts with DCs through multiple mechanisms, orchestrating the balance between tolerance to harmless antigens and pathogenic inflammation. Commensal bacteria and food antigens act via pathogen-associated molecular patterns on TLR-expressing IECs, promoting TSLP and TGF- β secretion to induce the differentiation of TolDCs. TolDCs further promote the generation of Foxp3⁺ Tregs and suppress Teffs in MLNs to maintain homeostasis. As key antigen capture sites, LysoDCs and CD11b⁺ dendritic cells within Peyer's patches utilize the Mincle-Syk axis to detect mucosal resident commensal bacteria, triggering IL-6 and IL-23 expression. Cross-regulation with Th17 cells and ILCs exquisitely maintains barrier integrity and intestinal immune equilibrium. Upon epithelial tissue damage or pathogenic invasion, DCs extend dendrites through the epithelial barrier to capture pathogens directly. Upon activation, mDCs trigger inflammatory responses and migrate to MLNs to suppress Treg function, enhancing Teff activity and initiating inflammatory cascades. DCs, dendritic cells; TLRs, Toll-like receptors; IECs, intestinal epithelial cells; TSLP, thymic stromal lymphopoietin; TGF- β , transforming growth factor β ; tolDCs, tolerogenic dendritic cells; Tregs, regulatory T cells; Teff, effector T cells; RA, retinoic acid; ILCs, innate lymphoid cells; LysoDCs, lysozyme-expressing DCs; TNF- α , tumor necrosis factor-alpha; mDCs, mature dendritic cells.

sensing through receptors such as Mincle in DCs triggers Syk-dependent production of IL-6 and IL-23, thus promoting intestinal barrier integrity through the activation of Th17 and ILC3 cells [51] (Figure 2).

In addition to controlling regional immunity within the intestine, intestinal DCs have also been identified as key mediators of microbiota-gut-brain communication [52]. Following microbial colonization, CD11b⁺CD11c⁺CD103⁺ DCs are able to migrate to the brain and thus mediate behavioral changes and impact brain neuroplasticity [53]. The chemotactic and metabolic signals instructing DC migration into the brain remain to be further identified [54]. Previous studies have shown that C-C motif chemokine ligand 2 (CCL2) [55], C-X-C motif chemokine ligand 10 (CXCL10) [56], and CCL19/21 [57] are involved in regulating the migration of DC subsets across the blood-brain barrier or into the brain parenchyma and are therefore likely involved in the trafficking of intestinal DCs to the brain. Moreover, increasing evidence indicates that specific gut microbial metabolites regulate the gut-brain axis through multiple pathways. For example, SCFAs

traverse the blood-brain barrier via the circulatory system, binding to G protein-coupled receptors (GPCRs) on the surfaces of neurons and glial cells within the central nervous system (CNS) to regulate neuronal excitability and the synthesis and release of neurotransmitters [58,59]. Indole-3-pyruvic acid (IPyA), a tryptophan metabolite, binds to the aryl hydrocarbon receptor (AHR) and crosses the blood-brain barrier, directly impacting nervous system function [60–63]. It is worth identifying the metabolic triggers that drive the gut-to-brain migration of DCs and developing novel therapeutic approaches targeting this process.

Moreover, specific bacterial species could display unique effects in modulating DC-mediated antitumor immunity. For example, *Lactobacillus intestinalis* exerts antitumor effects by recruiting DCs to the tumor microenvironment via NOD1/NF- κ B-dependent pathways [64]. Recent research revealed that a novel gut bacterial strain, *Hominenteromicrobium* YB328, significantly enhances antitumor immunity by activating CD103⁺CD11b⁺ DC migration, highlighting microbiota-DC interactions as promising therapeutic targets for disease treatment [65].

Metabolic Crosstalk between the Intestinal Microbiota and Dendritic Cells

The intestinal microbiota gives rise to various bioactive metabolites, such as SCFAs, bile acids and tryptophan derivatives, with diverse roles in shaping host immunity [66]. These microbe-derived metabolites are generated from dietary components, host compounds, or microbial metabolism. DCs serve as fundamental innate immune cells that not only capture and present microbiota antigens but also integrate intestinal metabolic signals for the fine-tuning of immune tolerance and inflammatory pathogenesis [67–69].

Short-chain fatty acids

SCFAs such as acetate, propionate, and butyrate are produced mainly through commensal gut bacterial fermentation of dietary fiber. SCFAs play essential roles in maintaining intestinal homeostasis and regulating immune responses [70,71].

SCFAs can activate G protein-coupled receptors such as FFAR2 (GPR43), GPR109A, and Olfr78, triggering intracellular signaling cascades such as the AKT and MAPK pathways and thereby widely modulating immune signaling, cell proliferation, and cytokine responses [72,73]. Accumulating evidence highlights how the SCFA-GPCR axis in DCs facilitates both immune defense and tolerance. Acetate enhances DC expression of *Aldh1a2*, which converts vitamin A into its metabolite retinoic acid (RA) through GPR43. The production of RA subsequently promotes IgA class switching and IgA production in B cells [74] (Figure 3). With respect to oral tolerance, butyrate and propionate exert anti-inflammatory effects primarily via GPR109A and GPR43, which suppress LPS-induced proinflammatory cytokines, including IL-6, IL-12p40, CCL3/4/5, and CXCL9/10/11, in human monocyte-derived DCs [75]. Additionally, high-fiber diets increase SCFA production, which involves GPR43 and GPR109A signaling to increase retinal dehydrogenase activity in CD103⁺ DCs, thereby promoting regulatory responses to food antigens [76].

Importantly, SCFA-GPCR signaling in DCs is essential for the maintenance of mucosal immune surveillance. GPR109A is a receptor for butyrate and niacin in the colon. GPR109A-mediated microbiota-DC interplay is critical for protection against colitis and colon cancer, as evidenced by increased severity of colonic inflammation and colon cancer in mice deficient in GPR109A [77]. Mechanistically, GPR109A signaling induces the anti-inflammatory function of colonic macrophages and DCs and therefore induces IL-10-producing T cell and Treg differentiation while stimulating epithelial IL-18 production (Figure 3). The anti-inflammatory and anticancer functions of butyrate and niacin via the GPR109A pathway have important implications for the clinical intervention of inflammatory bowel disease and colon cancer, although the detailed mechanisms underlying this dual role in preventing both inflammation and carcinogenesis remain to be further identified. It will be intriguing to elucidate the regional variations in GPCR expression patterns in distinct DC subsets along the intestinal tract and their functional relevance to homeostasis and diseases. The therapeutic potential of targeting specific SCFA-GPCR pathways in DCs also warrants further exploration for managing food allergies, inflammatory bowel diseases, and colorectal cancer.

SCFAs not only can regulate downstream pathways by binding to GPCR signaling but can also enter host cells, translocate to the nucleus, and inhibit histone deacetylases (HDACs) while activating

histone acetyltransferases (HATs). This enhances histone acetylation, relaxes the chromatin structure, and upregulates target gene expression [78,79]. Microbiota-derived butyrate selectively suppresses cDC2 development, leading to reduced expression of costimulatory molecules and impaired ability to activate T cells. While butyrate treatment increases H3K27 acetylation in IRF4^{hi} and IRF8^{hi} cell populations, the inhibition of HDAC3 could mimic the effect of butyrate on cDC development, suggesting that the effects of butyrate on cDC development likely depend on its role as an HDAC3 inhibitor. Further evidence is needed to directly elucidate epigenetic alterations, such as chromatin accessibility, histone modifications, DNA modifications, regulatory enzymes or RNA binding during key cDC development, or functional genes, such as *Irfs*, *Clec10a*, *Cd103*, and *Sirpa* [80]. The immunomodulatory effects of butyrate on DCs synergize with its ability to widely inhibit T and B-cell function. For example, butyrate promotes Treg development and suppresses intestinal inflammation via enhanced *Foxp3* *CNS1* (conserved noncoding sequence 1) enhancer accessibility [81]. Moreover, butyric acid and propionic acid act by inhibiting HDACs to upregulate specific microRNAs (miRNAs) that target the 3'UTRs of *Aicda* and *Prdm1* mRNAs. This reduces the expression of activated cytidine deaminase (*AID*) and B lymphocyte inducible protein 1 (*Blimp1*), thereby inhibiting class-switch DNA recombination, somatic hypermutation, and plasma cell differentiation, ultimately diminishing both intestinal and systemic antibody responses [82] (Figure 3). These findings establish SCFAs as potent regulators of DC-based immune networks with therapeutic potential for intestinal diseases. In addition, although SCFAs (such as butyrate) have been implicated in the treatment of colitis [83], studies indicate that oral and intraperitoneal administration of butyrate exert unexpectedly opposing effects on DSS-induced colitis [84,85]. Therefore, the optimal route and dose of SCFA delivery remains a clinical challenge considering the *in vivo* metabolite stability, tissue and cell selectivity, potential off-target effects, and heterogeneity of disease states.

Bile acids

Bile acids (BAs) are cholesterol-derived metabolites with potent roles in diverse physiological processes, such as nutrient absorption, glucose homeostasis, and energy metabolism [86], and thus widely participate in host-microbiome interactions and immune regulation [87,88]. BAs are synthesized in the liver as primary BAs and are subsequently modified by gut bacteria into secondary BAs. Various BA metabolites engage receptors such as the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1/TGR5) to regulate immune cell activity and function, including DCs [89].

The gut microbiota plays a central role in generating distinct BA metabolites that fine-tune DC-mediated intestinal immunity. The secondary bile acid 3 β -hydroxy deoxycholic acid (IsoDCA) enhances Foxp3⁺ Treg differentiation by diminishing the immunostimulatory capacity of DCs. IsoDCA reduces the expression of multiple genes related to antigen processing and presentation and inflammatory signal transduction by DCs, and the ability of IsoDCA to increase Treg generation depends on FXR expression in DCs [90] (Figure 3). In addition, *Clostridium scindens* converts primary intestinal bile acids into DCA via its 7 α -dehydroxylase. Upon binding to surface or intracellular receptors on pDCs, DCA activates the MyD88-dependent signaling pathway, restoring the capacity of

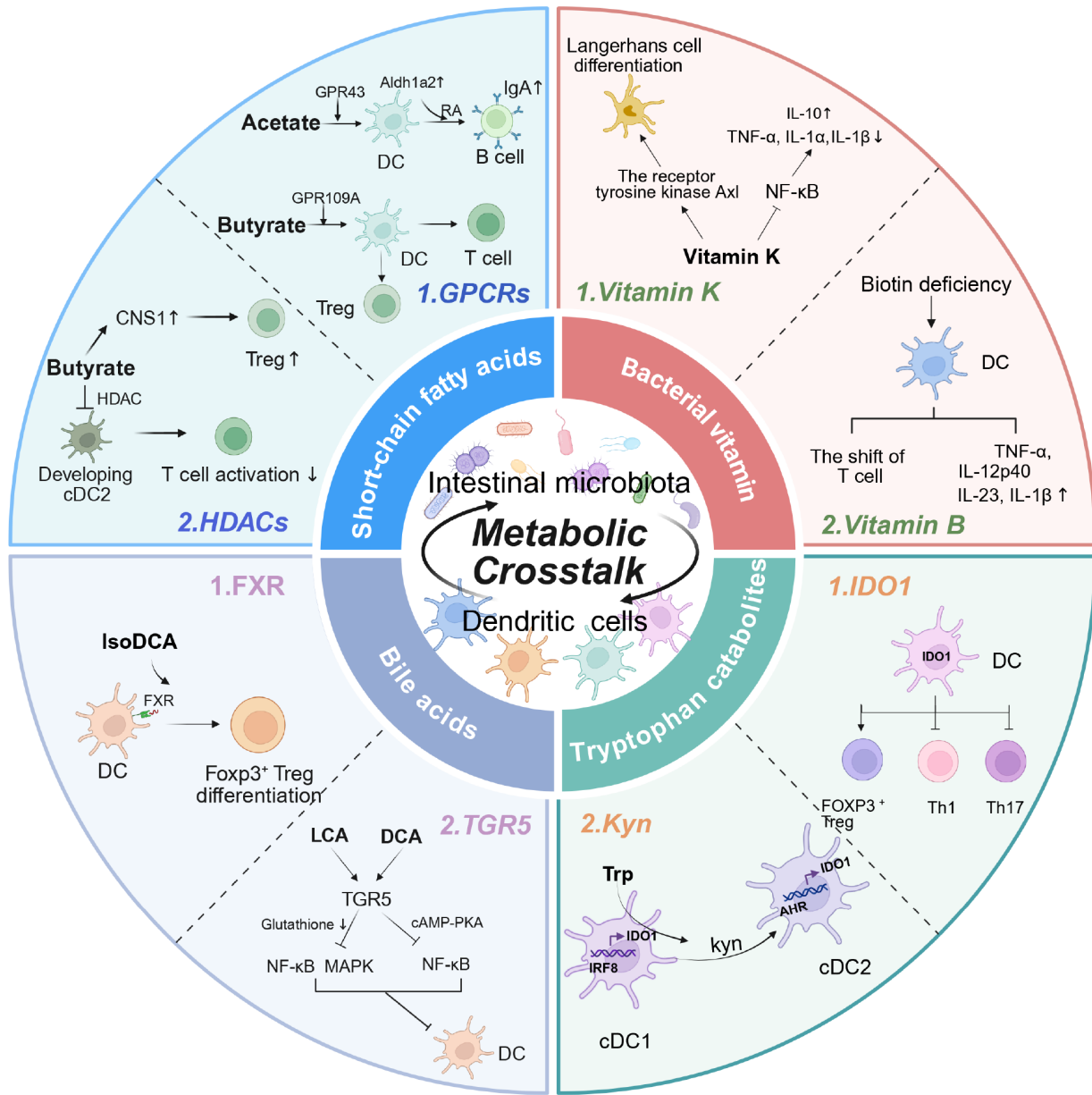


Figure 3. Metabolic crosstalk between the intestinal microbiota and DCs Microbe-derived metabolites (e.g., short-chain fatty acids, bile acids, tryptophan catabolites, and bacterial vitamins) modulate DC maturation, function, and immune regulatory properties through specific receptors or pathways, shaping host immune responses and intestinal homeostasis. (1) Short-chain fatty acids. Acetate and butyrate act on immune cells such as DCs and Tregs by binding to GPR43 and GPR109A, respectively, or inhibiting HDACs, thereby regulating immune cells. (2) Bile acids. IsoDCA promotes the differentiation of Foxp3⁺ Tregs by binding to FXR, while DCA and LCA bind to TGR5 receptors and inhibit NF-κB activity to regulate the function of DCs. (3) Tryptophan metabolites. IDO1 regulates the influence of DCs on the differentiation of Foxp3⁺ Tregs and Th1 and Th17 cells. Tryptophan can also be metabolized into kynurenine, which acts on cDC2s. (4) Bacterial vitamins. Vitamin K is involved in the differentiation of Langerhans cells and inhibits inflammation, whereas biotin deficiency promotes DC-induced proinflammatory T-cell responses. DCs, dendritic cells; GPCRs, G-protein-coupled receptors; Aldh1a2, aldehyde dehydrogenase 1 family member A2; HDACs, histone deacetylases; CNS1, conserved noncoding sequence 1; Treg, regulatory T cell; BAs, bile acids; FXR, farnesoid X receptor; TGR5, Takeda G protein coupled receptor 5; IsoDCA, 3β-hydroxy deoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; Trp, tryptophan; IDO1, indoleamine 2,3-dioxygenase; Kyn, kynurenine pathway.

pDCs to produce type I IFN. Type I IFNs further induce Ly6C⁺ monocytes to express IFN-stimulated genes (ISGs), thereby enhancing their antiviral response [91]. Similarly, gut bile acid metabolites directly promote RORγ⁺ Treg generation and maintenance via BA nuclear receptors, and genetic ablation of BA metabolic pathways in individual gut symbionts significantly decreases the

expansion of Treg populations [92]. Another study screened a library of bile acid metabolites and identified two distinct derivatives of lithocholic acid (LCA), 3-oxoLCA and isoalloLCA, which inhibit Th17 cell differentiation and increase Treg differentiation, respectively. The mechanisms of their regulatory role differ: 3-OxoLCA directly binds to the key transcription factor

retinoid-related orphan receptor- γ t (ROR γ t), whereas isoalloLCA promotes the production of mitochondrial reactive oxygen species (mitoROS) and increases Foxp4 expression via the intronic Foxp3 enhancer CNS3 [93]. Notably, a novel lymphoid-derived ROR γ t⁺ DC subset that critically orchestrates intestinal tolerance through peripheral Treg induction was recently identified, but the origins and functions of this subset remain unclear [94,95]. It is intriguing to explore whether distinct BA derivatives differentially regulate ROR γ t expression and stability to mediate subset-specific immune regulation.

Therapeutic strategies targeting BA metabolism and its interaction with the DC-centered intestinal immune system have emerged as promising strategies for treating immune-mediated disorders [96,97]. On the one hand, targeting BA synthesis and signaling has considerable protective effects on the modulation of intestinal inflammation. For example, IsoDCA-producing consortia (by engineering an IsoDCA-producing strain of *Bacteroides thetaiotaomicron*) increase the number of colonic ROR γ t-expressing Tregs in a CNS1-dependent manner, providing new clues for developing BA-dependent targeting strategies [90]. Restoration of intestinal BA metabolism increases colonic ROR γ t⁺ Treg pools and ameliorates inflammatory colitis [92,93]. Supplementation with gut microbiota-mediated secondary bile acids such as deoxycholic acid (DCA) and lithocholic acid (LCA) inhibits NF- κ B through TGR5 signaling, thereby suppressing DC activation and attenuating autoimmune pathogenesis [98,99]. FXR agonists, which are capable of regulating BA synthesis and inflammatory responses while improving intestinal barrier function, are currently under therapeutic development for IBD and metabolic disorders [100,101].

On the other hand, targeting BA absorption and tissue availability also has significant therapeutic potential. Probiotics can reduce ileal BA reabsorption and alter the gut microbiota composition by inhibiting the intestinal-hepatic FXR-FGF15 axis, although their effects on the BA pool and enterohepatic circulation remain to be investigated [102]. Clinical studies further indicate that bile acid preparations (e.g., UDCA) and sequestrants (e.g., colestipol) may alleviate Crohn's disease (CD) symptoms [103]. Overall, restoring bile acid metabolism and manipulating BA-microbiome-immunity interactions represent promising therapeutic avenues. Further elucidation of the metabolic and molecular mechanisms underlying BA-DC crosstalk will be essential for translating these insights into targeted clinical therapies.

Tryptophan catabolites

Tryptophan is obtained primarily from dietary proteins and is absorbed in the small intestine [67]. A variety of microbial species in the gut (e.g., *Escherichia coli*, *Proteus vulgaris*, *Clostridium perfringens*, etc.) can directly degrade tryptophan to indole and its derivatives, such as indole ethanol (IE), indole propionic acid (IPA), indole lactic acid (ILA), and indole acetic acid (IAA) [104]. These microbe-derived metabolites serve as critical mediators linking the gut microbiota to intestinal immunity.

Intestinal microbiota-derived tryptophan metabolites modulate intestinal immunity mainly by activating the pregnane X receptor (PXR) or AhR [105,106]. AhR is widely expressed on T cells, B cells, DCs and innate lymphocytes and responds to a variety of agonists and antagonists, including kynurenine, indoles and their derivatives [107]. AhR activation promotes the differentiation of monocytes into moDCs while inhibiting the differentiation of hematopoietic

progenitor cells into pDCs [108]. Indole-3-pyruvate (IPyA), an AHR activator, suppresses experimental colitis by diminishing the capacity of DCs in MLNs to induce IFN- γ production in T cells and promoting the accumulation of CD103⁺CD11b[−] DCs within MLNs [109]. The microbiota-AhR axis also orchestrates intestinal immune homeostasis by differentially regulating ILC subsets. AhR activation in ROR γ t⁺ ILC3s promotes IL-22 production, and AhR-dependent *Il22* transcription is required for balanced mucosal immunity, providing immune resistance to the fungus *Candida albicans* and providing protection against harmful inflammation [110,111]. In addition, AhR suppresses the expression of the IL-33 receptor ST2 by the transcription factor Gfi1, leading to reduced expression of the ILC2 effector molecules IL-5, IL-13 and amphiregulin and compromised antihelminth immunity in ILC2s [112]. The widespread regulatory capacity of AhR highlights it as a therapeutic target for balancing immune responses in inflammatory and infectious diseases.

IDO1 converts L-tryptophan into kynurenine, which confers immunoregulatory properties to DCs [113]. IDO1 expression or activity can be upregulated in DCs via multiple signals, such as the proinflammatory cytokine IFN- γ , TLR ligands, or TGF- β [114]. Gut CD103⁺ DCs express IDO1 to promote Foxp3⁺ Treg differentiation while suppressing Th1 and Th17 cell responses [115] (Figure 3). Inhibition or genetic deletion of IDO1 leads to impaired oral tolerance, exacerbated colitis, and enhanced T-cell proliferation, demonstrating its nonredundant function in mucosal homeostasis. The immunomodulatory function of IDO1 depends on its interaction with arginine metabolism. Specifically, Arg1-dependent polyamine production primes DCs for IDO1 phosphorylation, enabling subsequent Src kinase-mediated signaling that establishes the immunosuppressive property of DCs. This Arg1-IDO1 metabolic axis reflects how systemic metabolic integration contributes to DC functional plasticity in intestinal immunity [116].

IDO1 also mediates intercellular communication between cDC1s and cDC2s. Mature cDC1s express IDO1, exhibit heightened sensitivity to tryptophan metabolites, and can extend their immunological capabilities to cDC2s via L-kynurenine. Specifically, while steady-state CCR7⁺ cDC1s constitutively express IDO1 in an IRF8-dependent manner, cDC1-derived IDO1 is capable of activating the transcription factors AhR and RelB in cDC2s, thereby inducing IDO1 expression in cDC2s. This metabolic communication establishes a novel mechanism of transfer of tolerogenic functions from one cDC subset to another and represents a potential therapeutic target for treating autoimmune demyelinating diseases [117]. An in-depth exploration of the metabolic crosstalk between distinct intestinal DC subsets may thus offer novel perspectives for understanding microbiota-mediated immune tolerance and homeostasis.

The microbiota is actively involved in tryptophan metabolism, which potently programs immune cell function during infection and in tumors. For example, *Bacteroides ovatus*-derived indole-3-acetic acid promotes IL-22 secretion from DCs, exerting protective effects on trinitrobenzene sulfonic acid (TNBS)-induced colonic inflammation [118]. The tryptophan metabolite IAA, produced by *Lactobacillus reuteri* in the gut, alleviates colitis symptoms and inhibits colon tumor development by inducing IL-35 expression in immune-suppressive cells such as macrophages, T cells, and B cells [119]. *Lactobacillus plantarum* L168 and its metabolite, indole-3-lactic acid (ILA), increase IL-12 production by enhancing H3K27ac

binding at the enhancer regions of *Il12a*, thereby increasing antitumor CD8⁺ T-cell responses and ameliorating colorectal tumorigenesis [120]. Additionally, ILA can directly occupy the STAT3 phosphorylation site, leading to reduced levels of phosphorylated STAT3 and inhibiting the HK2 pathway, thereby downregulating glucose metabolism in cancer cells to suppress colorectal cancer [121]. Notably, specific microbial tryptophan metabolites can exert detrimental effects to aggravate disease pathogenesis. The intestinal bacteria *Peptostreptococcus anaerobius* degrade tryptophan to produce IDA. IDA acts as a ligand for AHR, activating the AHR-ALDH1A3-FSP1 signaling pathway, thereby inhibiting ferroptosis and promoting colon cancer cell proliferation and tumor progression [122]. These observations reveal how specific tryptophan metabolites influence disease progression through metabolic pathways, providing a mechanistic basis for microbiota-based interventions in immune-mediated diseases.

Bacterial vitamins

Vitamins can be acquired from dietary sources or synthesized by the gut microbiota. Dietary vitamins are preferentially absorbed through the small intestine and metabolized by distinct microbial species [123]. Vitamin A-derived all-*trans* retinoic acid (ATRA) instructs the transmigration of cDC2s into the intestinal epithelium by enhancing actomyosin contractility, endowing intraepithelial cDC2s with an immature phenotype and tolerogenic properties [124]. Vitamin E enhances the antitumor immunity of DCs by inhibiting pSHP1/SHP1 to enhance the cross-presentation of DCs and thus augments the responsiveness of immunotherapy [125]. Vitamin K supports TGF- β 1-dependent Langerhans cell differentiation and function via the receptor tyrosine kinase Axl but downregulates the immune activation marker CD86 during LC differentiation, thus playing a complex role in skin immunity [126]. Vitamin K2 protects against intestinal inflammation by inhibiting NF- κ B activation, reducing the levels of proinflammatory cytokines (TNF- α , IL-1 α , and IL-1 β) and increasing the levels of an immunosuppressive cytokine (IL-10) in colonic tissues [127,128]. Similarly, biotin (vitamin B7) deficiency enhances the inflammatory response in human DCs, leading to an increase in the proinflammatory cytokines TNF- α , IL-12p40, IL-23, and IL-1 β , as well as driving the shift of T cells to Th1/Th17 cells, suggesting an anti-inflammatory role of biotin in innate immune cells [129,130] (Figure 3).

Vitamin-mediated immune regulation remains largely unexplored. Variations in the gut microbiota composition, dietary nutritional status, and medication-induced microbiota alterations are indispensable factors that affect vitamin availability and metabolism. Future research on vitamin-mediated immune homeostasis, particularly specific vitamin sensing or utilization pathways in DC subsets, may provide new insights into microbiota-immunity crosstalk in the gastrointestinal environment.

Polyamines

Polyamines, including spermine, spermidine, and putrescine, are small polycationic compounds essential for mammalian cell growth, proliferation, and intestinal epithelial integrity [131]. These bacteria are absorbed mainly in the small intestine and synthesized in the lower gut by microbiota such as *Bacteroides* and *Fusobacterium* [132]. Polyamines potently regulate key processes, including cell differentiation, death, and tumor formation, via multiple mechanisms, such as influencing DNA replication, transcription,

translation, and posttranslational modification [133–135].

Polyamines are important in regulating myeloid cell function and activation in various contexts. Putrescine derived from commensal bacteria increases the abundance of anti-inflammatory macrophages in the colon [135]. Exogenous spermine supplementation prevents inflammatory DC function, likely by inhibiting glycolysis, and alleviates the development of psoriasis-like symptoms in mice [136]. Importantly, spermine can inhibit the JAK-STAT pathway induced by cytokines such as type I and type II interferons, IL-2, and IL-6, effectively curbing the abnormal activation of immune cells and autoinflammatory responses [137]. Spermidine derived from *Lactobacillus murinus* reduces type I IFN- α expression in pDCs by inhibiting K63-linked polyubiquitination of TRAF3, resulting in increased bowel movement in individuals with irritable bowel syndrome [138]. While multiple studies have confirmed their beneficial role in maintaining health, other studies have indicated that their activity may act as a catalyst for disease onset and progression. Further evidence is needed to elucidate the role of polyamines in regulating intestinal immune responses and their potential therapeutic applications.

Other metabolites

In addition to the abovementioned metabolites, several additional microbiota-derived metabolites or chemicals have been shown to modulate intestinal DC function. For example, the probiotic *Bifidobacterium bifidum* produces a cell surface polysaccharide (CSGG, β -glucan/galactosan) to induce Foxp3⁺ Treg differentiation through TLR2-expressing intestinal DCs. Notably, CSGG has demonstrated both *in vitro* efficacy in enhancing Treg activity and *in vivo* therapeutic potential in mouse models of experimental colitis [139]. Similarly, polysaccharide A (PSA) from *Bacteroides fragilis* exhibits anti-inflammatory properties by stimulating IL-10 production from intestinal Tregs, thereby maintaining mucosal immune homeostasis and protecting against viral encephalitis. Interestingly, duodenal and ileal pDCs and B-cell plasma blasts bind PSA with the highest intensity, indicating a nonredundant role for pDCs in mediating PSA-mediated immune tolerance [140]. *Lactobacillus* species and their metabolites also significantly influence intestinal DC function. Secreted factors and surface components from *Lactobacillus rhamnosus* drive DC polarization toward an anti-inflammatory phenotype [141]. Furthermore, the mouse commensal bacterium *Dubosiella new Yorkensis* plays an important role in rebalancing Treg/Th17 responses and improving mucosal barrier damage by producing propionate and L-lysine (Lys). Lys enhances immunotolerance in DCs by activating the metabolic enzyme IDO1 in an AhR-dependent manner, thereby promoting the catabolic degradation of tryptophan via the kynurenine pathway [142]. These findings collectively reveal how specific microbial components contribute to the complicated network of microbiota and immunity and underscore the translational potential of microbiota metabolites to orchestrate balanced DC immunity for immune defense and homeostasis.

Metabolite Synergy and Antagonism Network

Metabolites derived from the gut microbiota constitute a complex chemical network that interactively modulates the function of immune cells and intestinal homeostasis. For example, Indole, as a dietary metabolite of tryptophan, serves as the primary endogenous precursor of AhR ligands. Within the intestinal microenvironment,

it acts synergistically with SCFAs and secondary bile acids to modulate inflammation by reducing stress levels in epithelial cells and intestinal immune cells, thereby maintaining gut homeostasis [143]. Butyrate acts through HDAC inhibition to significantly increase the AhR recruitment efficiency to target gene promoters in the presence of tryptophan-derived AhR agonists. This amplifies AhR-mediated transcriptional regulatory effects [144]. Furthermore, the expression of the bile acid receptor FXR in intestinal epithelial cells is constrained by SCFAs derived from the neonatal microbiota under homeostasis. Conversely, elevated FXR expression promotes ferroptosis in necrotizing enterocolitis [145]. Thus, gut microbial metabolites constitute a sophisticated chemical ecosystem where synergistic and antagonistic interactions coexist. The multifaceted effects of these metabolites—whether additive, synergistic, or redundant—require further investigation. Elucidating these relationships is fundamental to understanding the maintenance of intestinal immune homeostasis and crucial for developing novel immunomodulatory strategies targeting microbial metabolites, such as therapies for inflammatory bowel disease and autoimmune disorders.

Conclusions and Perspectives

In summary, metabolic crosstalk between the intestinal microbiota and DCs serves as a fundamental mechanism for immunobiological homeostasis by maintaining tolerance against harmful self-antigens and food materials and preventing unwanted inflammatory injury. Disruption of the microbiota-immune balance upon pathogenic infection or tissue damage shifts the tolerogenic response toward a persistent and inflammatory response and even results in the development of inflammatory disorders. Elucidating these complex networks not only advances our understanding of gastrointestinal health versus disease but also opens new therapeutic avenues for developing microbiota metabolite-targeted therapeutic strategies.

In both healthy individuals and those with IBD, the microbiome and its metabolites exhibit significant interindividual variability and generally limited bioavailability. Additionally, the effects of most gut microbiota-derived metabolites on immune cells are highly context-dependent, highlighting their dynamic and plastic functional potential in maintaining homeostasis and modulating inflammation. This complexity presents not only a research challenge but also vast opportunities for further exploration.

These challenges highlight the critical need to employ multi-dimensional approaches to elucidate the complex interplay between microbial metabolism and DC immunobiology. Specifically, integrated multiomics platforms, CRISPR-based functional genomics, high-resolution intravital imaging, and spatial metabolomics will be crucial for molecular mapping of metabolite sensing and processing pathways in distinct DC subsets. Moreover, characterization of microbe-derived immunomodulators and their context-dependent roles in determining DC fate and function will provide new insights into mucosal homeostasis versus inflammatory cascades. In addition, while the current understanding of this field largely relies on mouse models, there is an urgent need to accelerate clinical translation and deepen mechanistic investigations to enable the development of more precise and effective therapeutic interventions. These findings elucidate fundamental host-microbiota crosstalk mechanisms governing intestinal health and disease pathogenesis, ultimately enabling the development of novel DC-targeted immunotherapies for inflammatory bowel diseases and

related immune-mediated disorders.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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