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REVIEW ARTICLE

Immunomodulation by foods and microbes: Unravelling the molecular tango

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Abstract

Metabolic health and immune function are intimately connected via diet and the microbiota. Nearly 90% of all immune cells in the body are associated with the gastrointestinal tract and these immune cells are continuously exposed to a wide range of microbes and microbial-derived compounds, with important systemic ramifications. Microbial dysbiosis has consistently been observed in patients with atopic dermatitis, food allergy and asthma and the molecular mechanisms linking changes in microbial populations with disease risk and disease endotypes are being intensively investigated. The discovery of novel bacterial metabolites that impact immune function is at the forefront of host-microbe research. Co-evolution of microbial communities within their hosts has resulted in intertwined metabolic pathways that affect physiological and pathological processes. However, recent dietary and lifestyle changes are thought to negatively influence interactions between microbes and their host. This review provides an overview of some of the critical metabolite-receptor interactions that have been recently described, which may underpin the immunomodulatory effects of the microbiota, and are of relevance for allergy, asthma and infectious diseases.

KEYWORDS
AhR, GPCRs, metabolites, microbiome, nuclear receptors

1 | INTRODUCTION

Human mucosal surfaces and body cavities harbour diverse communities of commensal microbes that play essential roles in regulation of host metabolic responses, epithelial barrier function, immune education and immune regulation.[1–4] Microbial-derived factors are integral components of the molecular circuitry that regulate immune and metabolic functions required for host physiology and survival. These host effects are partially induced by activation of host pattern recognition receptors to microbial-derived danger signals, but increasingly the role of secreted bacterial metabolites in shaping host immune function is being recognized.[5–8] Immunoregulatory bacterial metabolites can trigger host G protein-coupled receptors (GPCRs), aryl hydrocarbon receptor (AhR), nuclear hormone receptors such as the farnesoid X receptor (FXR) or can directly modulate gene expression through epigenetic mechanisms.

Abbreviations: AhR, Aryl Hydrocarbon Receptor; ARNT, AhR Nuclear Translocator; CaS, Calcium-Sensing Receptor; COVID-19, Coronavirus Disease 2019; FXR, Farnesoid X Receptor; GPCR, G Protein-Coupled Receptor; IFN, Interferon; ILC, Innate Lymphoid Cell; LXR, Liver X Receptor; MAIT, Mucosal-Associated Invariant T cells; NR, Nuclear Receptor; PPAR, Peroxisome Proliferator-Activated Receptors; PXR, Pregnane X Receptor; SCFAs, Short-Chain Fatty Acids; TLR, Toll-Like Receptor; TSLP, thymic stromal lymphopoietin SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2; VDR, Vitamin D Receptor.

Importantly, many immunoregulatory bacterial metabolites are derived from their metabolism of dietary ingredients (e.g. fibre, tryptophan), linking diet and lifestyle to protection from immune-mediated disorders via microbial mechanisms. Microbial fermentation of dietary components in vivo potentially generates thousands of molecules, some of which regulate immune and metabolic functions. These in turn are thought to protect against aberrant inflammatory processes or hypersensitive responses, but also promote effector immune responses that efficiently eliminate pathogens, such as SARS-CoV-2.[9–11] While individual microbes, individual dietary components and individual metabolites are certainly important, the overall community functional capacity and community metabolic outputs that underpin interactions with the host immune system are perhaps more relevant with regard to understanding disease risk. A low-risk microbe-diet configuration may generate sufficient levels of several regulatory metabolites that are associated with protection from aberrant inflammatory responses. In contrast, a high-risk microbe-diet configuration may consistently generate multiple pro-inflammatory metabolites that may contribute to a higher risk of inappropriate immune reactivity (this model is illustrated in Figure 1). Indeed, recent changes in dietary habits and microbiota composition, especially evident in obese individuals, have resulted in reduced levels of immune regulatory metabolites that are expected and evolutionarily hardwired into immune cell decision-making processes.[12] The lack of immune regulatory molecules may lead to a hypersensitive immune system that does not respond appropriately thus leading to a chronic state of inflammation that culminates in organ damage and disease for an increasing number of people.[13–17] In this review, we will describe the immune cell receptor systems that recognize secreted microbial-derived metabolites and highlight their relevance to immune-mediated disorders. We have deliberately excluded pattern recognition receptors from this review as these have been extensively reviewed elsewhere.[18]

2 | DIETARY EFFECTS ON MICROBE-HOST IMMUNE INTERACTIONS

Malnutrition is well recognized as an important risk factor for poor immunological responses, especially related to infectious diseases. However, obesity has more recently also been identified as a risk factor for severity of infectious diseases, including influenza and coronavirus. In addition, obesity is associated with a range of chronic inflammatory non-communicable diseases, such that obesity is now associated with higher mortality worldwide compared with being underweight.[19] A simple excess in calories does not explain these negative effects on the immune system. Rather, the transition to reduced diversity, low-quality, highly processed, high-energy diets have altered the metacommunity, its processes that underpin assembly and activity of the human microbiome and, consequently, increased risk of inappropriate and uncontrolled immune responses that damage host tissues and function.[20] Indeed, weight loss is associated with improvements in microbiota diversity and intestinal permeability, suggesting the negative effects associated with obesity are reversible, at least in part.[21–23]

Consumption of a higher diversity of fruits, vegetables and fermented foods are associated with a reduced risk of atopic disorders and asthma in children, potentially mediated in part by

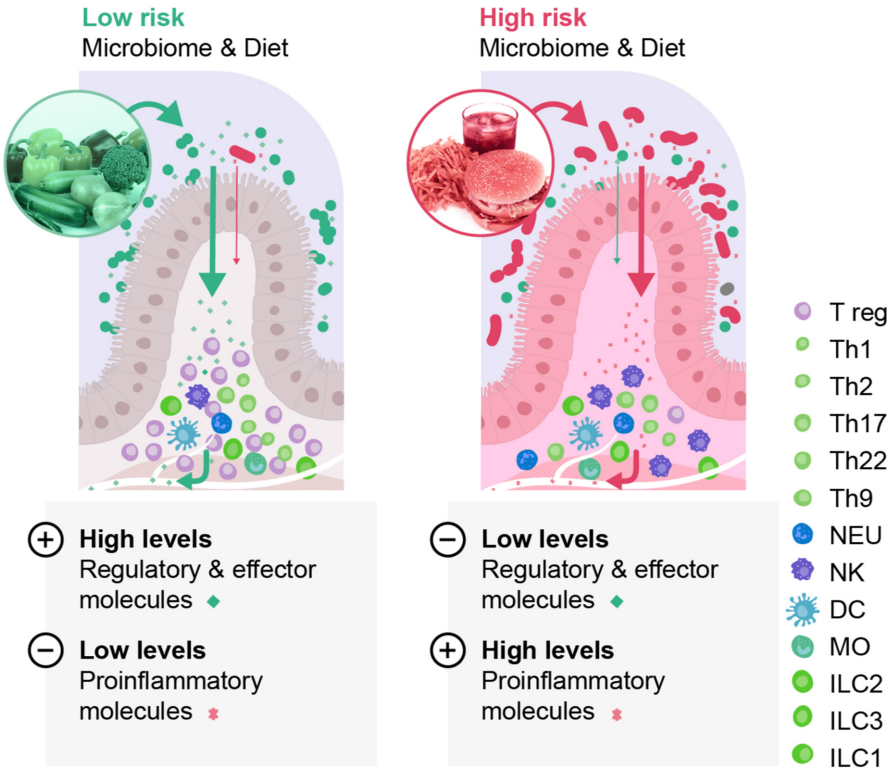

FIGURE 1 Schematic model illustrating the concept of a high-risk versus a low-risk configuration of microbiota-dietary interactions that influence risk of immune-mediated disorders

microbial-derived butyrate and propionate.[24,25] Children of mothers who consumed lower levels of fruits, vegetables and yoghurt during pregnancy, had a similar risk of allergic outcomes as children with the filaggrin gene mutation, demonstrating that diet was just as important as a genetic risk allele for prevention of this immune-mediated disorder.[26] In addition, adults who more regularly consumed plant-based or pescatarian diets seemed to have lower odds of developing severe COVID-19.[14,27,28] However, the specific plant-based substrates (e.g. fibre type, fatty acids, polyphenols) that are responsible for these positive associations are unknown. A number of studies have focussed on supplementing intake of fibre to compensate for shortfalls in regular consumption. However, one recent study in human volunteers showed that high fibre consumption did not result in the expected microbiota and immune benefits, potentially due to a lack of pre-existing microbes that can process non-digestible carbohydrates into immune modulatory metabolites.[29] In addition, there are many different types of fibres and the optimal fibre-bacterial strain combinations that generate immune-modulatory compounds are not yet known.[30,31]

It is thought that a sufficiently large microbial community of diverse genomic inputs allows buffering and redundancy in case certain community members are lost, thereby maintaining important metabolic and host protective functions. Microbial communities that could quickly, and appropriately, shift their functional repertoire in response to diet change would have subsequently enhanced human dietary flexibility and survival. However, recent surveys of microbial composition from industrialized human cohorts are significantly different compared with traditional cohorts, with many species disappearing from industrialized populations.[32,33] For example, *Lactobacillus reuteri* (*L. reuteri*) was regularly detected in multiple human studies performed around the 1960s and is still found today in many individuals living in rural Papua New Guinea but is absent in all control samples from individuals in the USA.[34] Overall, species diversity and richness has been shown to be reduced by about one-third in Americans compared with Malawians or Amerindians.[35] Importantly, antibiotic-driven depletion of the gut microbiome in humans, with associated impacts on secondary bile acid and tryptophan metabolism, disrupts the induction of antibody responses to influenza vaccination possibly by driving inflammatory signalling in innate immune cells in a manner consistent with age-associated changes in immune responses.[36] Interestingly, altered tryptophan metabolism and bile acid metabolism were also recently shown to be associated with elevated levels of multiple pathobionts and pro-inflammatory cytokines in patients with severe and fatal outcomes to SARS-CoV-2 infection.[9] In contrast, less severe clinical outcomes to infection were associated with SCFAs, IL-17A and clusters of microbes with previously recognized immune regulatory effects (e.g. *Ruminococcus*, *Roseburia*, *Bifidobacterium* and *Faecalibacterium*). Disturbed tryptophan metabolism and increased levels of alarmins such as thymic stromal lymphopoietin (TSLP) remained evident in Long COVID patients linking microbial dysbiosis with significant metabolic reprogramming, impaired epithelial barrier function and ineffective immune responses.[37–41] Alterations in microbial tryptophan and bile acid metabolism have also been described in subgroups of patients with asthma or food allergy.[42]

3 | IMMUNOREGULATORY BACTERIAL METABOLITES

Due to the complexity of the human microbiome and its vast coding potential, there are likely many bacterially produced molecules that can influence immune cell activity and immune regulation. Indeed, one systematic analysis identified over 3000 small molecule biosynthetic gene clusters within the human microbiome.[43] Remarkably, the majority of these gene clusters have never been studied or even previously described.

One example that clearly illustrates the metabolic promiscuity underpinning co-evolution of host and microbial metabolism is tryptophan.[44–46] Microbial-derived tryptophan metabolites such as indole-3-acetic acid, indole-3-propionic acid and indole-3-aldehyde trigger host AhR protective responses such as IL-10, IL-22 and type I IFNs secretion that improve the epithelial barrier and limit local inflammatory responses in murine models.[47–49] Microbial-derived indoles can also inhibit TH17 CD4 T cell differentiation through interactions with RORγt. In addition, the microbiota-derived metabolites taurine, histamine and spermine were shown to modulate NLRP6 inflammasome signalling, epithelial IL-18 secretion, and anti-microbial peptide (AMP) profiles in mice.[50] Treatment of human dendritic cells with the bacterial-derived 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) reduced anti-inflammatory cytokine secretion and the number of Treg cells, suggesting that this metabolite impedes immune tolerance.[51] In contrast, short-chain fatty acids (SCFAs) are potent immunomodulators that promote IL-10 secretion by dendritic cells, influence Treg numbers and effectiveness, influence bone marrow haematopoiesis, reduce effector T cell activity, improve epithelial barrier, and inhibit mast cell and ILC2 activation.[52–55] Fibre consumption or SCFA administration in murine models protects against colitis, inflammatory arthritis, respiratory syncytial virus infection and allergic diseases. SCFAs exert effects on the host immune system via binding to G protein-coupled receptors (GPCRs) such as GPR41, GPR43 and GPR109A, and via epigenetic modifications. Lastly, nicotinamide production by *Akkermansia muciniphila* was shown to be protective in a murine model of amyotrophic lateral sclerosis.[56]

In addition to bacterial-derived metabolites binding to immunoregulatory receptors, unconventional lymphocyte subpopulations can directly recognize microbial-derived metabolites as antigens. For example, human immature intrathymic mucosal-associated invariant T (MAIT) cells recognize bacterial-derived 5-(2-oxopropylideneamino)-6D-ribitylaminouracil (5-OP-RU) that acts as an antigen and stimulator for the MAIT cells, via a major histocompatibility complex Class Ib molecule MR1.[57] This finding not only demonstrated that microbial-derived metabolites control development of mucosal targeted T cells but also challenges our traditional distinction between exogenous and self-antigens. Similarly, another unconventional T

cell lineage, invariant natural killer T cells (iNKT cells) respond to bacterial glycolipid antigens.[58] The functional objectives of T cell responses to the microbiota are not completely understood and are likely context-dependent. However, the malleability of T cells in response to microbiota metabolism presents an opportunity to edit T cellularity, identity and functionality by utilizing microbiota-driven molecular pathways to promote human health.

For the remainder of this review, we will focus in more detail on the three host receptor systems that have been best studied for mediating bacterial-derived metabolite effects on immune cell function and activity. These receptors are located on the cell membrane (GPCRs), within the cell cytoplasm (aryl hydrocarbon receptor) or within the cell nucleus (nuclear receptors).

4 | G PROTEIN-COUPLED RECEPTORS

GPCRs are involved in mediating a large range of cellular events in response to external stimuli and serve as means of communication between the external and internal environments of the cell.[59] GPCRs are an extensive family of cell-surface proteins that represent the largest family of membrane proteins in the human genome.[60] Over 800 GPCRs have been identified to date but many remain orphan receptors as their ligands and function are still unknown.[61] GPCRs share a common structure that is characterized by 7 transmembrane domains, an extracellular amino terminus and an intracellular carboxyl terminus.[62] The transmembrane domains of GPCRs are composed of 25–35 amino acid residues and are alpha-helical in conformation, connected to adjacent transmembrane domains via alternating intracellular and extracellular loops.[63] Upon ligand binding, the GPCR becomes activated and stabilized in a conformation that allows it to interact with its associated heterotrimeric G protein. This binding allows the GDP bound to the Gα subunit of the G protein to be exchanged for GTP.[64] The binding of GTP to the Gα subunit causes the G protein to dissociate into its Gα and Gβγ subunit components that subsequently initiate distinct downstream signalling activities (Figure 2). The intracellular signalling cascade induced by G protein activation can include cAMP or phosphatidylinositol pathways, depending on the α subunit type ($G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q}$ or $G_{\alpha 12/13}$). Studies have identified multiple microbes and microbial-derived metabolites that can interact with human GPCRs as agonists or antagonists.[65–67] Their α subunit type binding is summarized in Figure 3.

GPR41 and GPR43 (also known as free fatty acid receptor 3 [FFA3] and FFA2, respectively) are activated by bacterial-produced SCFAs.[68] SCFAs are some of the most well-studied bacterial metabolites and consist of fatty acids containing aliphatic tails of <6 carbon atoms.[69] These carboxylic acids, which include acetate, butyrate and propionate, are produced as end-products from the bacterial fermentation of complex carbohydrates and the digestion of protein and peptides that avoid being digested and absorbed in the small intestine.[70] The highest concentrations of short-chain fatty acids are found in the proximal colon.[71] Here, these metabolites can cross the intestinal epithelium and enter the cell by diffusion or are absorbed using specific transporters and can be transported into the bloodstream to travel to organs and tissues distant to the gut.[69,72] SCFA activation of murine and human neutrophils via

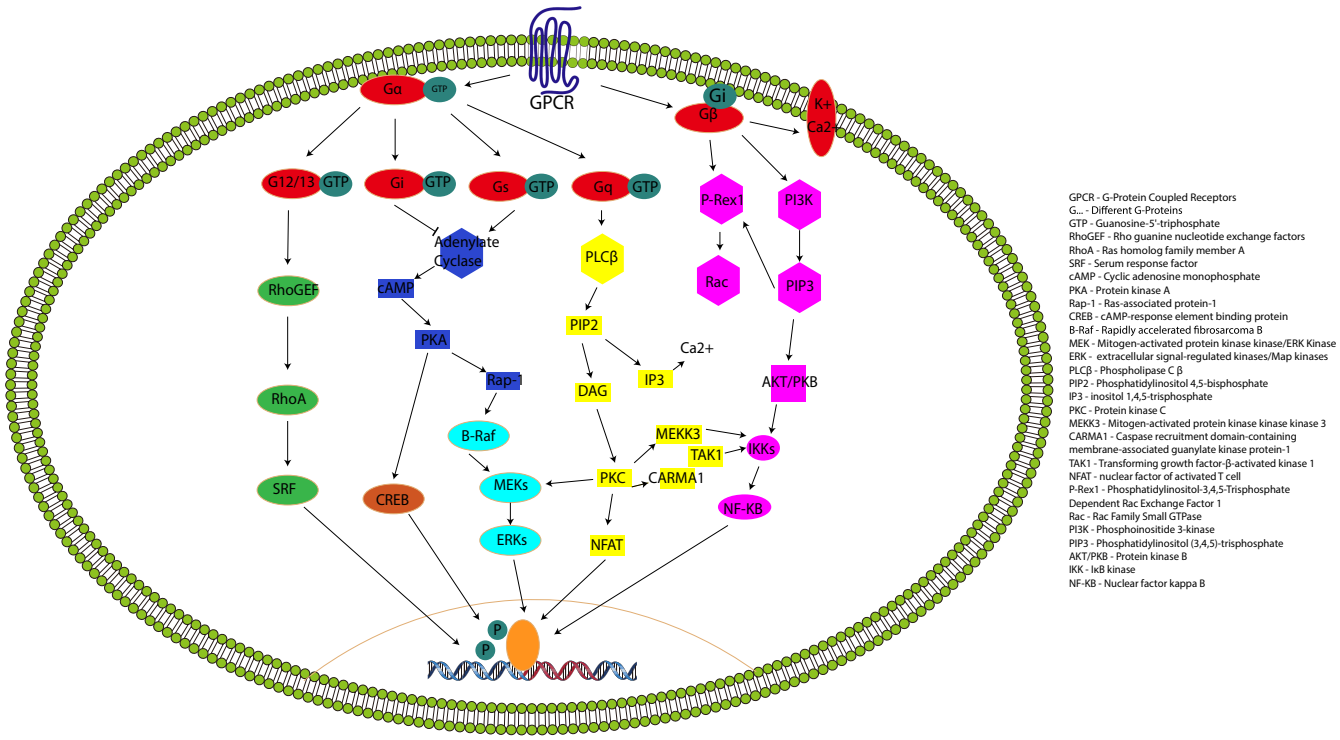

FIGURE 2 GPCR signalling. Following stimulation by their specific ligands, a conformational change causes the G-Proteins to disengage from the GPCR and create a signal cascade dependent on the Gα subunit that is activated

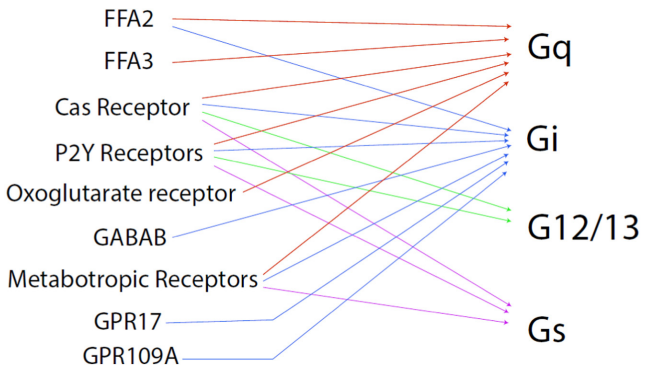

FIGURE 3 Gα subunit usage by different GPCRs

GPR43 triggers chemotaxis, as well as promoting superoxide and IL-1β production.[73,74] Murine ILC3 upregulate IL-1R via GPR43 leading to IL-22 production following activation by IL-1β.[75] Dendritic cell GPR43 activation results in the production of BAFF and A2ALD1a2, which support B cell IgA secretion in mice.[76,77] Type 2 macrophages produce increased TNFα levels and demonstrated increased bactericidal activity following GPR43 activation.[78] GPR109a has been shown to be activated by bacterial-derived butyrate and niacin.[79] GPR109a activation promotes anti-inflammatory properties in macrophages and dendritic cells in murine models and enables them to induce differentiation of Treg cells and IL-10-producing Tr1 cells.[80]

The four known histamine receptors (H1R-H4R) are GPCRs and have been shown to be triggered by bacterial-derived histamine.[7,81] Activation of H2R can influence a range of immune cell subsets, including mast cell degranulation, the response of dendritic cells to microbial ligands, iNKT cell responses to lipid antigens, proliferation and cytokine production from T cells and antibody secretion by B cells.[82–85] Human TH1 and TH2 cells preferentially express H1R and H2R, respectively, which influences cytokine secretion and proliferation.[86] The H4R receptor modulates chemotaxis in dendritic cells and regulates the activation of T cells.[87,88] An increased abundance of histamine secreting microbes, especially *Morganella morganii*, was observed within the gut of adult asthma patients, while histamine secretion from gut microbes could influence immune responses in the murine lung.[89,90] In addition to histamine, a wide range of microbes can produce biogenic amines and polyamines within the human gut.[91] The calcium-sensing (CaS) receptor has been shown to be stimulated by spermine, spermidine and putrescine and these bacterial-derived metabolites can influence airway inflammation in murine models.[92,93] The CaS receptor and GPR139 can also be activated by L-tryptophan, which can be produced by microbes.[94–96]

The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is an agonist of the metabotropic GPCR $GABA_B$ (GPR51) and can be produced by bacterial species.[97,98] The activation of $GABA_B$ on human leukocytes has been shown to interfere with chemotaxis induced by chemokine receptors and reduce production of TNF-α by macrophages.[99] All metabotropic glutamate receptors have been shown to interact with L-Glutamic Acid, which can be produced by bacteria.[100,101] Activation of metabotropic receptors on murine mast cells influences gene expression of pro-inflammatory molecules such as IL-6 and CCL2.[102] Human T cell adhesion, chemotactic migration, cytokine secretion and gene expression are also affected by the activation of metabotropic receptors.[103]

GPR17 can be stimulated by the nucleotide sugars uridine diphosphate, UDP-galactose and UDP glucose, which can be produced by bacteria.[104,105] Knockout of GPR17 has been shown to influence TH2, TH17 and TH1 cytokine expression in murine models.[106] The P2Y14 receptor (GPR105) has also been shown to be activated by the same nucleotide sugars as well as bacterial-derived UDP-glucuronic acid and UDP N-acetyl-glucosamine.[107–110] P2Y14 activation has a chemoattractant effect on monocytes/macrophages, as well as on human neutrophils and dendritic cells.[111,112] P2Y14 can also influence degranulation of human mast cells and suppresses T cell proliferation.[113,114] Bacterial-derived uridine diphosphate and uridine triphosphate can interact with multiple different P2Y receptors.[115] The activation of P2Y receptors promotes chemotaxis and efferocytosis (the identification, isolation and engulfment of apoptotic cells) in human macrophages, neutrophils and dendritic cells by acting as "find me" signals and upregulating expression of phagocytotic receptors.[116,117] P2Y11R also blocks neutrophil apoptosis.[118]

Succinate is an important metabolic intermediate in human cells and microbes.[119] The succinate receptor (GPR91) has been shown to influence the chemotaxis of human immature DCs while also playing a role in enhancing the production of the pro-inflammatory cytokines TNF-α and IL-1β.[120,121] Succinate receptor knockout murine mast cells showed a hyperreactive phenotype, with effects in a contact dermatitis model.[122]

The G2A receptor, also known as GPR132, is activated by microbiota-encoded N-acyl amides.[123] This receptor is highly expressed in murine macrophages and lymphoid tissue and is a member of the stress-inducible ovarian cancer G protein-coupled receptor 1 family of GPCR.[124] The endogenous ligand for the G2A receptor is unknown; however, the microbiota-encoded N-acyl amide N-3-hydroxypalmitoyl glycine, commonly referred to as Commendamide, has been shown to activate it.[123] The G2A receptor has been implicated in murine models of both autoimmune disease and atherosclerosis.[65]

The oxoglutarate receptor (GPR99) is activated by α-ketoglutaric acid, which can be bacterial-derived.[125,126] α-ketoglutaric acid has been shown to have a positive effect on histone demethylation, resulting in the promotion of T cell differentiation but inhibits murine M1 and enhances M2 polarization.[127,128]

5 | ARYL HYDROCARBON RECEPTOR

The aryl hydrocarbon receptor (AhR) is a ligand-activated cytosolic receptor, which belongs to Pern-Arnt-Sim (PAS) superfamily.[129] It was originally identified as a sensor of xenobiotic chemicals, in particular, aromatic (aryl) hydrocarbons from which the receptor derives its name.[130] When AhR is in a latent or non-DNA-binding state, it is present in the cytoplasm and associated with the 90 kDa molecular heat shock protein 90 (hsp90), p23 and hepatitis B virus X-associated protein (XAP2/AIP/Ara9).[131] Hsp90 masks AhR's nuclear localization

sequence (NLS) which retains AhR in the cytoplasm and it chaperones a high-affinity ligand-binding conformation of the AhR.[132] When AhR binds with its ligand, the AhR/Hsp90 complex translocate to the nucleus where Hsp90 is exchanged for the partner protein AhR nuclear translocator (ARNT).[133] The nuclear-localized, ligand-bound AhR/ARNT heterodimer recognizes and promotes transcription from dioxin- or xenobiotic-responsive elements (DREs/XREs), typified by the xenobiotic metabolizing enzymes cytochrome P4501A1 and the glutathione S-transferase Ya subunit.[134] The aryl hydrocarbon receptor repressor (AhRR), a basic helix–loop–helix (bHLH/PAS) protein is also recognized by AHR/ARNT.[135] The AhRR shows high sequence similarity with the AhR in the N-terminal region but diverges significantly at the C-terminus and does not have ligand binding or transactivation domains. It is thought that in vivo the AhRR is expressed in response to AhR ligands and subsequently functions to down-regulate AhR target genes by sequestering ARNT and competing for DRE sequences in the promoters of target genes.[135] Along with recognition of DREs by the AhR/ARNT complex it also interacts with other transcriptional regulators to control the expression of target genes (non-canonical pathway). For example, NF-κB induces AhR expression and AhR subsequently regulates NF-κB signalling.[136] AhR activation and signalling are summarized in Figure 4.

The best described microbial-derived metabolites that activate AhR are the indole products of microbial tryptophan metabolism. These include indole, tryptamine, skatole, indole-3-pyruvate, indole-3-lactate, indole-3-acrylate, indole-3-propionate, indole-3-acetamide, indole-3-acetate, indole-3-ethanol, indole-3-aldehyde and indole-3-acetaldehyde.[137] In addition, bacterial virulence factors and quorum sensors (e.g. phenazines, naphthoquinone and malassezin) can activate the AhR.[138,139] Most recently, the SCFA butyrate has also been shown to activate the AhR.[140] A list of microbial species known to secrete AhR ligands is shown in Table 1.

AhR is mainly expressed within barrier organs such as the skin, intestine, lung and associated immune cells, where AhR plays an important role in development and regulation of both innate and adaptive immunity. Multiple murine models suggest an important role for the AhR in maintaining the functional properties of Foxp3 Tregs, in particular the T cell immunoglobin and ITIM domain (TIGIT) + Foxp3+ Treg cells that express the highest levels of AhR relative to other Treg populations.[161–163] IL-27 drives AhR expression in IL-10 producing Tr1 cells where AhR cooperates with STAT3 to induce expression of the immunoregulatory ectonucleotidase CD39.[164–166] In addition, AhR plays a role in transdifferentiation of murine TH17 cells into Tregs.[167] However, AhR can also enhance TH17 cell differentiation and IL-22 secretion suggesting that specific ligands may have divergent effects within different microenvironments and cell differentiation stages.[168] Indeed, AhR-deficient murine dendritic cells fail to promote Treg cell differentiation but instead drive TH17 cell generation in vitro.[169] Importantly, AhR activation has been shown to be involved in the induction of murine CD4 + CD8αα + double-positive intraepithelial lymphocytes (DP IELs), which display regulatory functions associated with the induction of tolerance to dietary antigens.[170] Similarly, AhR signalling contributes to the persistence of murine tissue-resident CD8+ memory cells (TRMs) within the skin, supporting their protective role against microbial challenge.[171]

6 | NUCLEAR RECEPTORS

Nuclear receptors (NRs) are a family of ligand-activated transcription factors that regulate numerous physiological processes such as metabolism, reproduction, inflammation, as well as the circadian rhythm. NRs sense changes in lipid metabolite levels to drive differential gene expression, producing distinct physiologic effects.[172] NRs

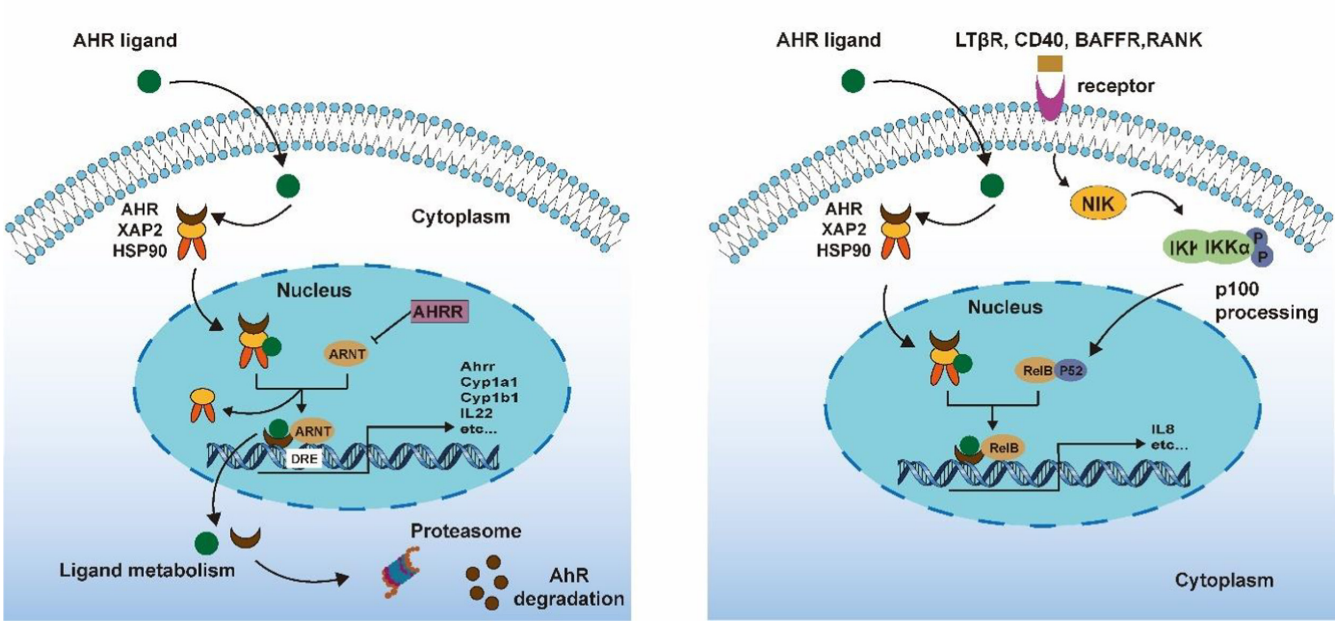

FIGURE 4 Mechanisms of canonical (left panel) and non-canonical (right panel) AhR signalling

TABLE 1 Microbial species associated with production of AhR ligands

Bacteria	AhR ligands
Lactobacillus reuteri	Indole derivative[47,141]
Lactobacillus murinus	Indole derivative[141]
Lactobacillus taiwanensis	Indole derivative[141]
Bacillus alvei	Indole derivative[142]
Clostridium novyi	Indole derivative[143]
Clostridium limosum	Indole derivative[144]
Clostridium tetani	Indole derivative[143]
Corynebacterium acnes	Indole derivative[145]
Enterococcus faecalis	Indole derivative[146]
Bacteroides thetaiotaomicron	Indole derivative[147]
Bacteroides sp.	Indole derivative[148]
Citrobacter sp.	Indole derivative[149]
Escherichia coli	Indole derivative[150]
Flavobacterium sp.	Indole derivative[151]
Fusobacterium sp.	Indole derivative[152]
Haemophilus influenza	Indole derivative[153]
Kleibsella planticola	Indole derivative[154]
Shigella flexneri	Indole derivative[155]
Vibrio cholera	Indole derivative[156]
Lactobacillus bulgaricus OLL1181	Not yet identified AhR ligands[157]
Kleibsella pneumonia	Indirubin, Indigo[158]
Malassezia	Trypthantrin[159]
Propionibacterium freudenreichii ET-3	1,4-dihydroxy-2-naphtoic acid[160]
Malassezia	Malassezin[159]
Malassezia	Indirubin[159]
Providencia stuartii	Indirubin[158]

share a common architecture of an N-terminal ligand-independent activation domain (AF2) followed by a DNA-binding domain (DBD), a flexible hinge region (Hinge) and a ligand-binding domain (LBD) composed of 12 α-helices (α1-α12).[173] NRs that respond to bacterial-derived ligands are summarized in Figure 5.

Farnesoid X receptor (FXR) is a bile acid-activated nuclear receptor.[174] As a ligand-activated transcription factor, FXR binds to DNA either as a monomer or as a heterodimer with retinoid X receptor (RXR, NR2B1) to regulate the transcription of target genes.[175] FXR is expressed within the human intestinal tract but also at other sites including the lung.[176,177] Bacterial modified secondary bile acids, such as deoxycholic acid and lithocholic acid, are FXR agonists, while supernatants from in vitro bacterial cultures also possess FXR ligands.[178,179] FXR-RARα signalling in murine mucosal dendritic cells supported food allergen-specific IgE and IgG1 production, while allergic diarrhoea can be attenuated by FXR agonists due to their antisecretory effects in colonic epithelial cells.[180,181] Ursodeoxycholic acid treatment of OVA-sensitized mice prior to OVA aerosol challenge significantly reduced eosinophilic airway inflammation via FXR signalling in dendritic cells.[182] Similarly, the FXR ligand chenodeoxycholic acid attenuates murine allergic airway inflammation by inhibiting TH2 cytokine secretion.[183]

Pregnane X receptor (PXR), a critical xenobiotic-sensing nuclear receptor, is expressed predominantly in the gastrointestinal tract and liver, but has also been shown to play an important role in murine and human skin where activation by environmental pollutants comprises epidermal barrier function favouring a TH2/Th17 response that resembles atopic dermatitis.[184,185] Bacterial-modified bile acids are PXR ligands, while bacterial-derived tryptophan metabolites such as indole-3-acetamide and indole-3-acetic acid also activate PXR with significant effects on epithelial barrier function in the murine gut.[186–188] PXR-deficient mice exhibit an exaggerated T lymphocyte proliferation with increased CD25 expression. Furthermore, PXR-deficient lymphocytes produce more IFN-γ and less IL-10.[189]

Peroxisome proliferator-activated receptors (PPARs) form a small family of ligand-activated transcription factors belonging to the nuclear receptor superfamily, which consists of 3 isotypes that are known to be involved in diverse biologic processes, including immune and inflammatory responses.[190] Microbial linoleic acid-derived fatty acids and conjugated linoleic acids are potent PPARα and PPARγ agonists.[191,192] More recently, butyrate and propionate have been identified as PPARγ agonists in human intestinal epithelial cells.[193] PPARγ signalling is important in regulating murine T cell-mediated responses by inhibiting effector T cell responses, while supporting Treg cells.[194,195] In addition, PPARγ signalling suppresses mast cell activation and TLR-induced NF-κB phosphorylation in human dendritic cells.[196–198]

Vitamin D receptor (VDR) is a nuclear hormone receptor and transcription factor expressed in a variety of tissues, including the intestines, adipose tissue and liver, as well as many immune cell subsets.[199] In addition to vitamin D, the bacterial-derived secondary bile acid lithocholic acid is a physiological VDR ligand, which has been shown to influence human and murine TH1 lymphocyte activation.[200,201] Interestingly, gut microbiota composition was significantly altered in intestinal epithelial VDR conditional knockout mice, while a genome-wide association study in humans identified associations between overall microbial variation and individual taxa with the VDR gene.[202,203]

Liver X receptors (LXR)α and LXR β are members of the nuclear receptor superfamily that regulate the expression of genes involved in lipid, glucose and cholesterol metabolism and homeostasis.[204] While LXR has been well described as a negative regulator of murine macrophage cytokine secretion, no microbial ligands have been discovered to date that are selective LXR ligands.[205]

7 | CONCLUSIONS AND FUTURE DIRECTIONS

The studies described in this review demonstrate that the different types of metabolites generated by microbes in the gut can have a profound impact on immune regulatory and immune effector

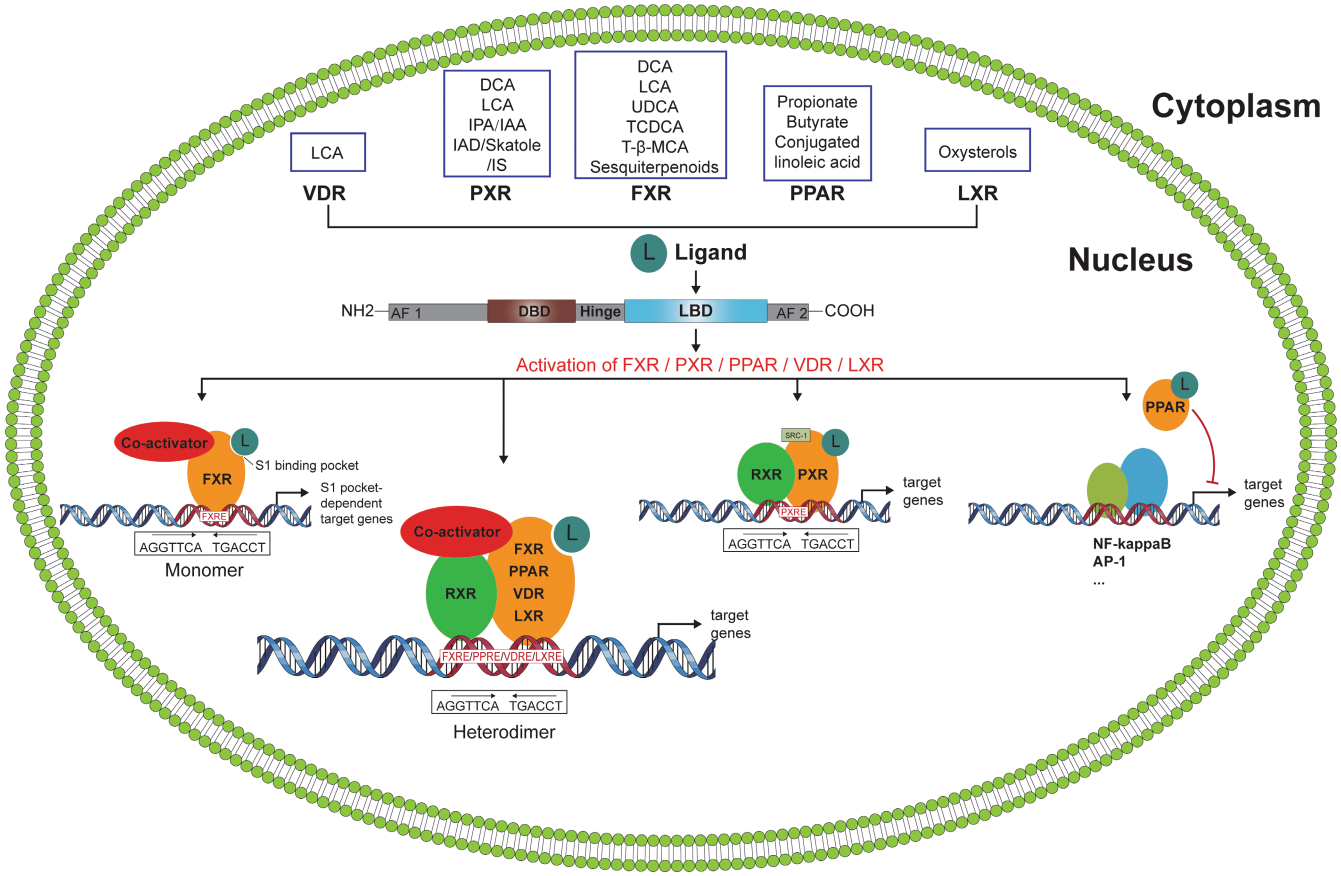

FIGURE 5 The different nuclear receptors are illustrated

functions. The structural similarities and overlaps that exist between microbiota-derived metabolites and endogenous signalling molecules are surprising, but this allows for relatively uncomplicated signalling molecules produced by the microbiome to impact more complex cellular interactions within the host. The immune response to bacteria should not be considered simply as a form of host defence but also represents a variety of intimate interactions with important symbiotic physiological effects on the host. Virtually all known cells with immunological functions (e.g. dendritic cells, epithelial cells, ILCs, T regulatory cells, effector lymphocytes, NKT cells and B cells) can be influenced directly or indirectly by microbial factors. However, interactions between the host and microbiota are almost certainly bidirectional, with species- and strain-specific behaviours shaped by the genetic background and microenvironmental niche in which they occur. Microbial factors are clearly evolutionarily hardwired into the molecular circuitry governing immune cell decision-making processes, but we have only discovered a relatively small number of metabolites thus far that contribute to this intimate and sophisticated inter-kingdom dialogue. In addition to identifying the metabolites themselves, there are also major gaps in our understanding of the mechanisms that integrate microbiota-derived signals into host immune pathways.

While BMI and (un)healthy dietary patterns have consistently been shown to be related to specific microbiota configurations, many of the strongest associations have been with poorly characterized microbes and often there is little or no information available on their specific molecular interactions within the host. In addition, due to the low resolution of dietary questionnaire data, the complexity of dietary patterns, nutrient–nutrient interactions and incomplete knowledge on the clustering of healthy/less healthy food items, it is often challenging to disentangle the independent associations of single foods with microbial species. Thus, future studies should endeavour to investigate beyond correlations to provide a functional basis for understanding causation. This is critically needed as in many cases it remains unclear whether and, if so, to what extent patterns of microbial taxonomical or functional dysbiosis actually drives rather than merely reflects associated patterns of immune reactivity.

Identifying the missing metabolites critical for immune development and regulation will substantially impact our understanding of the communications platform used by the immune system to interact with our microenvironment and will provide us with new tools to modify this communication when necessary to improve immune health. Indeed, given the malleability of the human microbiome, its integration into the immune system and its responsiveness to diet, makes it a highly attractive target for therapeutic and nutritional intervention. New studies focussed on understanding how specific dietary interventions impact the microbiota to generate immunoregulatory metabolites will be critical to develop effective diets that improve human immune health and prevent aberrant inflammatory responses.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

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