



MICROBIAL METABOLITES AS REGULATORS OF HOST IMMUNITY: MOLECULAR PATHWAYS, IMMUNE HOMEOSTASIS, AND DISEASE PROGRESSION

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ABSTRACT

Microbial metabolites have become a key mediator of host-microbial dialogue, connecting microbial activity to the regulation of the immune system, maintenance of tissue integrity, and disease pathogenesis. This review synthesizes current evidence on the major immunoregulatory metabolite classes, including short-chain fatty acids, tryptophan derivatives, secondary bile acids, polyamines, vitamins, and microbial lipids, and examines the molecular pathways through which they influence host immunity. Special emphasis is placed on G-protein-coupled receptor signaling, signaling of aryl hydrocarbon receptors, bile acid receptors, inflammasome pathways, epigenetic regulation and immunometabolic reprogramming. The review also examines the impact of microbial metabolites on the regulation of macrophage, neutrophil, natural killer, T-cell and B-cell function, as well as supporting epithelial barrier function, mucosal tolerance, colonization resistance and immune balance in the periphery. Dysregulated metabolite profiles are associated with diseases of the intestine, autoimmune, respiratory, cardiometabolic, neurological, infectious and malignant diseases, but effects are highly receptor- and tissue-dependent and dose- and host physiology-dependent. The following are examples of translation opportunities: metabolites as biomarkers, postbiotic approaches, receptor-targeted interventions, and modulation of immunotherapy responses. The next steps will rely on causal validation, standardisation of multi-omics, mechanistic precision and personalised microbiome-directed immunomodulation.

Keyword: microbial metabolites, host immunity, immune homeostasis, microbiota-immune signaling, precision immunomodulation

Introduction

The human microbiota forms a complex ecosystem that constantly interacts with host tissues and plays an essential role in the regulation of much more than microbial colonization. Microbial communities in the gastrointestinal, skin, respiratory and other mucosal surfaces have an impact on nutrient utilization, integrity of the epithelium, metabolic activity and protection against pathogenic organisms, and disturbances of these communities are increasingly associated with a variety of disease states (Hou et al., 2022). The immune regulatory function is in particular among these functions, since the immune system needs to be tolerant to beneficial microorganisms while at the same time being able to respond efficiently to pathogens entering the body. Throughout the lifetime, immune development, thresholds of activation and tissue-specific responses are influenced by reciprocal interactions between resident microorganisms and immune components (Ansaldi et al., 2021). Disruption of this bidirectional interaction between the microbiota and host immunity can impair immune tolerance and inflammatory control, contributing to chronic inflammatory, autoimmune, metabolic, and infectious diseases (Zheng et al., 2020).

The immune impact of the microbiota is increasingly shown to be more complex and depends on more than just the amount or type of microbes. The metabolome produced by the functional activity of the microbial communities is chemically diverse and can be used to create a molecular interface between microorganisms and host cells. Thus, a host-centered understanding of the metabolome is required, as the biological effect exerted by a microbial product is dependent on the host's production, availability, exposure of the tissue and interaction with host signaling systems (Yamada & Palm, 2025). Metabolites can be classified into several categories that modulate host physiology and disease-related processes, such as short-chain fatty acids, tryptophan derivatives, secondary bile acids, polyamines, vitamins and microbial lipids (Sittipo et al., 2019). They may function locally in mucosal sites or enter systemic circulation, which can link microbial metabolism with immune responses at remote sites. It is important to note the multiple effects of microbial metabolites, including receptor activation, transcription regulation, epigenetic modification, cell metabolism, and modulation of inflammatory signaling, making microbial metabolites active rather than passive by-products of microbes (McCarville et al., 2020).

These interactions have a number of physiological and pathological implications. Changes in the gut microbiome and metabolites have been linked to vascular and renal mechanisms regulating blood pressure, and thus suggest that gut microbiota signals could be linked to systemic immune-metabolic pathways (O'Donnell et al., 2023). Microbial metabolites have direct impacts at the cellular level on various aspects of T-cell biology, such as differentiation, functional programming, persistence and effector responses, strongly linking microbial metabolism with adaptive immunity (Tran et al., 2025). Such mechanistic understanding has also stimulated quests for the manipulation of microbial metabolites or their targets in the host as a potential biomarker and therapeutic approach for immune-mediated diseases (Zeng et al., 2025).

Although great strides have been made, the field remains highly fragmented, both at the level of individual metabolites, signaling pathways, immune-cell types and in the context of disease. Dysbiosis of microbial communities has been linked to disease in myriad publications, but the causality of specific microbial metabolites to molecular targets, immune reprogramming, loss of homeostasis and disease progression has yet to be fully understood. The effects are complex and may differ depending on the tissue and its context, the concentration of the metabolite, the expression of receptors, the host physiology and the disease stage. This means that there is a need for enhanced integration of molecular, cellular and disease-level evidence.

The purpose of this review is to make a critical synthesis of the main classes of immunoregulatory microbial metabolites and understand the molecular pathways by which they interact with host immunity. It also explores their role in the function of innate and adaptive immune cells, their involvement in immune homeostasis and host defense mechanisms, and their role in disrupting metabolite-mediated signaling pathways leading to disease progression. A final review discusses new therapeutic opportunities based on metabolites, and mechanistic and translational priorities needed to progress towards precision microbiome-directed immunomodulation.

2. Major Microbial Metabolites with Immunoregulatory Functions

The microbiota alters immune activity locally and systemically through the production of a wide-ranging and diverse array of bioactive compounds produced by microbial metabolism. The short-chain fatty acids (SCFAs) are some of the most well characterized immunoregulatory metabolites, including acetate, propionate and butyrate. SCFAs are mainly generated by fermentation of dietary carbohydrates in the intestine by bacteria, linking diet, microbial metabolism and epithelial and immune functions. They exert biological effects such as enhancing the integrity of the intestinal barrier, controlling inflammatory response and modulating the differentiation and activity of various immune-cell populations (Mann et al., 2024). The microbial metabolism also affects the expression of immune-related genes and cell phenotypes through an epigenetic mechanism by inhibiting histone deacetylases (HDACs) to varying extents (Wang et al., 2025).

Another important pathway of microbiota-immune communication is through the metabolism of the essential amino acid tryptophan. The intestinal flora converts dietary tryptophan into indole and its structurally related compounds that have significant signaling properties. These metabolites are involved in interaction with host pathways, such as the aryl hydrocarbon receptor pathway and are implicated in regulation of mucosal immunity, epithelial function, inflammatory regulation, and antitumour responses. Microbial tryptophan metabolism can thus cause a change in the immune homeostasis-pathological inflammation balance (Hou et al., 2023).

A unique example of metabolites that are structured by both host and microbes is the bile acids. Primary bile acids produced by the host are deconjugated and transformed by microorganisms to create a variety

of secondary bile acids. They serve as signaling molecules that can help regulate innate and adaptive immune responses via the bile acid-sensitive receptors and other cellular targets (Lee et al., 2024). Altered bile acid metabolism by microbes can impact the composition of immune cells in the intestine, inflammatory signaling and intestinal epithelial physiology, which can be linked to chronic intestinal inflammation and tumorigenesis (Cai et al., 2022).

The other metabolically active groups are the polyamines, which include putrescine, spermidine and spermine, and have immunological relevance. They participate in cell growth, mitochondrial activities, protein production and metabolic programming, which allows them to modulate the activation and differentiation of immune cells. The endogenous-polyamines / microbiota-associated polyamine metabolism, in turn, may influence immunometabolic conditions during homeostasis and inflammation (Mahalingam & Pandiyan, 2024). Vitamin metabolism is also affected by microorganisms. B-group vitamins act as metabolic cofactors and can also regulate immune-cell development and activity, thus connecting the availability in the diet and from microbial sources to immune competence of the host (Yoshii et al., 2019).

Microbial lipid metabolism adds to the range of immunologically active molecules. Modifications and production of fatty acids, sphingolipids and other lipid species by bacteria can have a permissive role in membrane biology, metabolic signaling, epithelial physiology and immune responses. These lipid-based interactions provide an example of how microbes can produce signals that can affect processes outside the intestinal lumen (Brown et al., 2023). Ultimately, the immunological significance of microbial metabolites is not only determined by their chemical nature but also by the rate of their production, the concentration in the gut, their rate of absorption, their ability to reach the tissue and their interactions with host cells. The intestinal metabolic environment is a vital component of host defense, as it can alter immune-cell responses during infection and also play a role in the integrity of the epithelial barrier (Adams et al., 2024).

There are several important connections between microbial metabolism and host immunity, including SCFAs, tryptophan derivatives, secondary bile acids, polyamines, B vitamins, and microbial lipids. Their effects on the immune system are influenced by microbial production and host exposure, and thus offer a biochemical basis for metabolite-mediated immune modulation, immune homeostasis, and immune deregulation in diseases. The main microbial metabolite classes, their origin and main immunological activities are summarized in Table 1.

Table 1. Major microbial metabolites and their immunological functions

Metabolite class	Representative metabolites	Main origin	Major immune role	Key references
Short-chain	Acetate, propionate,	Fiber	Barrier support;	Mann et al., 2024;

fatty acids	butyrate	fermentation	immune regulation	Wang et al., 2025
Tryptophan derivatives	Indoles	Tryptophan metabolism	AhR signaling; mucosal immunity	Hou et al., 2023
Secondary bile acids	Microbial bile acid derivatives	Primary bile acid conversion	Immune and inflammatory regulation	Lee et al., 2024; Cai et al., 2022
Polyamines	Putrescine, spermidine, spermine	Microbial and host metabolism	Immunometabolic regulation	Mahalingam & Pandiyan, 2024
B vitamins	B-family vitamins	Diet and microbial synthesis	Immune-cell support	Yoshii et al., 2019
Microbial lipids	Fatty acids, sphingolipids	Microbial lipid metabolism	Membrane and immune signaling	Brown et al., 2023

3. Molecular Sensing and Signaling Pathways

Microbial metabolites are recognized by an interconnected network of membrane, cytosolic and nuclear sensors that convert microbial metabolic activity into cellular responses. Microbial signals are continually integrated by epithelial and immune cells of the intestine while differentiating homeostatic signals from signals that elicit inflammatory and defensive responses (Wan et al., 2023). The intestinal barrier is especially significant as it is the first interface where receptors encounter molecules derived from the microbiota, which can affect barrier function and mucosal immunity without being directly invaded by the microbes (Eshleman & Alenghat, 2021).

One of the major classes of metabolite sensors is the G-protein coupled receptors (GPCRs). The availability of nutrients and bacterial fermentation is linked to the regulation of inflammation and to the activation of the receptors FFAR2, FFAR3 and HCAR2 by SCFAs and other microbial products. These receptor-mediated responses are dysregulated in inflammatory conditions of the intestines, highlighting the significance of the diet–microbiota–metabolite axis in controlling immune responses (Melhem et al., 2019). Canonical intestinal GPCRs are not the only ones involved in metabolic recognition. The gut microbiota-associated metabolite phenylacetylglutamine can signal through the adrenergic receptors and is an example of how microbial metabolites can tap into host receptor systems to produce systemic physiological effects (Nemet et al., 2020).

Another key pathway that is responsive to metabolites is the aryl hydrocarbon receptor (AhR) pathway. The indole derivatives produced by microbes can activate AhR and affect epithelial barrier integrity and mucosal immunity (Scott et al., 2020). The effects of AhR are highly dependent on cellular and physiological context, and beyond its role in the environment and in metabolism, it serves as a sensor of ligand exposure that coordinates transcriptional programs that regulate immune cell differentiation, inflammatory activity, and tissue homeostasis (Rothhammer & Quintana, 2019).

Microbial metabolite sensing is expanded to nuclear and membrane receptor networks by bile acid signaling. The gut-liver axis is involved in the regulation of inflammatory and metabolic signaling that can be impacted by the microbial transformation of the bile acid pool, which alters the binding availability of bile acids to gut-liver axis receptors such as FXR and TGR5 (Yan et al., 2025). These interactions represent a 'targetome' wider than the individual receptor pathways in which microbial metabolites interact with multiple host proteins. It is, therefore, critical to map these metabolite–target relationships to understand how metabolically different microbial products converge to the same cellular program or have tissue-specific effects (Zheng et al., 2022).

Innate inflammatory system is also engaged by microbial signals. Microbial metabolic disturbances may affect purinergic signaling and inflammasome activation, such as the P2X7R/NLRP3 axis, which relates to the alteration of microbial metabolism and inflammatory responses (Chen et al., 2025). This relationship is especially significant in the context of severe systemic inflammation, where disruptions in the microbiota, microbial products, and inflammatory pathways can create a mutually reinforcing cycle, impacting immune activation and disease progression (Xu et al., 2025).

The ability to signal downstream of metabolite sensing goes beyond chromatin regulation to include cellular metabolism. Transient exposures of host cells to microbiota-derived metabolites can lead to long-term changes in host-cell function through changes in DNA and histone modification, chromatin accessibility and transcriptional programs (Lei et al., 2025). Metabolite-dependent metabolic reprogramming not only can change the utilization of nutrients, but also can help to change the functional state of immune cells and the activity of mitochondria, which are important and have implications for antitumour immunity and the response to immunotherapy (Lu et al., 2025).

These pathways are seldom used alone. Microbial metabolites may impact inflammatory signaling, cellular metabolism, epigenetic states, and tumour-associated immune responses all at once, potentially limiting or promoting tumorigenesis in the context of metabolites and tissue (Ullah et al., 2025). The SCFA signaling pathways are also involved in host energy metabolism and immune regulation, and the nature of substrates and metabolites entering these pathways is determined by cross-feeding by microorganisms. These events show metabolite sensing as a dynamic network that is influenced by the microbial ecology and host metabolic status and not a set of independent ligand–receptor events (Réka et al., 2025).

GPCRs, AhR, nuclear receptors, inflammasome-associated machinery, epigenetic mechanisms and immunometabolic networks are all mechanisms for decoding microbial metabolites. The interactions between these systems are translated into context-specific transcriptional and immune responses to microbial metabolism, thus connecting the dots between metabolite exposure and host physiology. The principal receptors involved in sensing metabolites and the resulting immune effects are summarized in Table 2.

Table 2. Major microbial metabolite-sensing pathways in host immunity

Microbial signal	Host sensor/pathway	Main target	Principal effect	Key references
SCFAs	FFAR2, FFAR3, HCAR2	Epithelial and immune cells	Inflammatory control	Melhem et al., 2019
Tryptophan metabolites	AhR	Epithelial and T cells	Barrier and immune regulation	Scott et al., 2020; Rothhammer & Quintana, 2019
Bile acids	FXR, TGR5	Intestinal and hepatic cells	Metabolic-inflammatory control	Yan et al., 2025
Phenylacetylglutamine	Adrenergic receptors	Cardiovascular cells	Systemic signaling	Nemet et al., 2020
Microbial metabolic signals	P2X7R/NLRP3	Innate immune cells	Inflammasome activation	Chen et al., 2025
SCFAs and other metabolites	Epigenetic pathways	Immune cells	Gene-expression reprogramming	Lei et al., 2025

4. Microbial Metabolite Control of Immune-Cell Function

Microbial metabolites influence the activation state, differentiation, trafficking and effector programs of a variety of innate and adaptive immune cell populations. Microbiota-derived signals, due to the tight association between functional polarization of macrophages and local environmental parameters and metabolic status, are especially responsive. Macrophage responses to microbial signals are context-dependent and can be polarized toward different phenotypes, depending on the organism, the stimulus, and the tissue, demonstrating a plasticity of macrophage responses to microbial inputs (Wang et al., 2020).

In addition, intestinal metabolites affect macrophage polarization by affecting intracellular signaling, energy metabolism and the production of cytokines, leading to the resolution of inflammation or the maintenance of inflammatory activity (Lun et al., 2024).

Neutrophils are involved in a dynamic interaction with the microbiota as well. Neutrophils and microbial communities interact during neutrophil development, recruitment, activation and antimicrobial function, and neutrophils contribute to the composition of microbial communities at mucosal surfaces (Zhang & Frenette, 2019). Butyrate shows the context-dependency of this interaction, as it can inhibit excessive inflammatory effector activity, neutrophil migration and activation. This restraint may help decrease tissue damage and inflammation of the mucosal tissues, especially in the context of inflammatory bowel disease pathology, which is associated with uncontrolled responses from neutrophils (Li et al., 2021).

Another innate immune population that can be regulated by metabolites is natural killer cells. In addition to myeloid cells, butyrate can also inhibit the activity of human natural killer cells, such as cytotoxicity and production of inflammatory cytokines, suggesting that SCFAs may moderate immune responses outside of myeloid cells (Zaiatz-Bittencourt et al., 2023). This effect is biologically relevant because natural killer cells contribute to antiviral defence, tumour surveillance, and inflammatory regulation; therefore, metabolite concentration and biological context may determine whether these effects are protective or potentially detrimental.

Microbial metabolites exert strong influences on CD4⁺ T-cell differentiation and function, thus shaping adaptive immune responses. In the intestine, CD4⁺ T cells combine microbial and host-derived signals to control intestinal inflammation, tolerance and tissue homeostasis, and microbial signals regulate the balance between the intestinal effector and regulatory subsets (Ma et al., 2025). In particular, metabolites may play a significant role in regulating the Th17–regulatory T-cell axis. The availability of these metabolites can influence the acquisition of pro-inflammatory (Th17) or immunosuppressive (Treg) properties of CD4⁺ T cells and thus the immune balance (Calvo-Barreiro et al., 2023).

The immune regulation by metabolites is further complicated by B-cell regulation. Microbiota-derived products can modulate the activity of regulatory B cells beyond just affecting the production of antibodies, via receptor-dependent signaling pathways. Microbial metabolites have been found to directly regulate disease-modifying regulatory immune programs by enhancing the anti-inflammatory functions and reducing the arthritis-associated inflammation of regulatory B cells through induction of the aryl hydrocarbon receptor (Rosser et al., 2020).

Microbial metabolites thus are not specific for one lineage of the immune system, but orchestrate immune responses between macrophages, neutrophils, natural killer cells, T cells and B cells. The effects are dependent on the metabolite involved, on the cellular repertoire of receptors, on the metabolic state of the cells, on the tissue environment and on the inflammatory context. The cell-specific responsiveness is a mechanism by which changes in microbial metabolism can alter the balance of host defense, immune

tolerance and pathological inflammation. Microbial metabolites control immunity by modulating the immune cell functions of innate and adaptive immunity. Their cell-specific and context-dependent effects can either regulate negative inflammatory responses or turn beneficial immune responses on or off; thus, immune-cell programming is a key mechanism that connects the metabolism of microbes with health and disease. The microbial metabolites that target major immune cells and their overall impact on immunity, immune tolerance and inflammation are summarized in Figure 1.

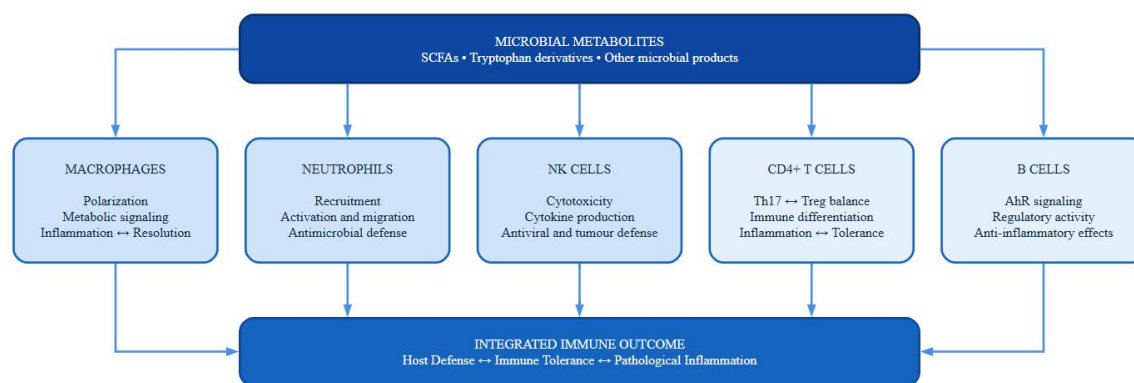


Figure 1. Microbial metabolite regulation of innate and adaptive immune-cell functions

5. Maintenance of Immune Homeostasis and Host Defense

Mucosal immune homeostasis is a dynamic interplay between microbes, epithelium and the immune system. Intestinal epithelial cells are not only a physical barrier, but also incorporate microbial signals and modulate the production of antimicrobial peptides, protection against mucus and the activity of immune cells. The ability to tolerate the presence of commensal microorganisms and yet still be able to respond to pathogens and tissue damage is controlled through this interface (Kayama et al., 2020). This balance is further regulated in a coordinated way by mucosal adaptive immunity, which involves responses from both T and B cells, to prevent excessive inflammatory responses, maintain immunological surveillance, and provide barrier protection (Wang et al., 2019).

The microbial metabolites play a direct role in maintaining barrier function via effects on epithelial integrity, tight-junction organization, mucus production and inflammatory signaling. Production of SCFAs and other bacterial metabolites can sustain energy requirements of epithelial cells and functions of epithelia associated with the gut and other immune compartments; while dysregulations in the metabolic activity of the gut bacteria may increase epithelial permeability and expose underlying immunity to luminal antigens. Metabolic imbalance may then, in turn, shift a protective microbiota–epithelial relationship to a pro-inflammatory one that leads to intestinal inflammation (Gasaly et al., 2021). Host-cell metabolism is also essential for the defense, as the activation of the immune system must involve rapid changes in nutrient utilization, mitochondrial function and biosynthetic pathways in order to allow the activation of antimicrobial effector mechanisms (Pernas, 2021).

Another basic, protective function of the host is colonization resistance. Co-colonization of the host by resident microorganisms helps prevent establishment of pathogens by several mechanisms: competition for nutrients and ecological niches, production of inhibitory compounds, modification of the local environment and interactions with host immunity. The level of protection achieved is based on a combination of community structure, host and environmental factors; therefore, disruption of community structure or metabolic activity can make them more susceptible to invasion by pathogens (Woelfel et al., 2024). Communication by soluble metabolites is not the only mode of microbiota communication. Biologically active microbial components carried by bacterial extracellular vesicles are able to interact with immune and physiological systems at distant sites and play roles in inter-organ signaling, such as bone homeostasis (Liang et al., 2025).

Further systemic immune homeostasis is achieved by the communication between the intestine and distant organs. The gut–liver axis is of particular interest due to the fact that the liver is continuously exposed to metabolites and microbial products from the intestine via the portal circulation. These interactions along this axis may affect hepatic metabolism and immunity, linking gut microbial activity to the rest of the organ systems such as the brain, cardiovascular system, and other organs (Anand & Mande, 2022). The fact that these metabolites can be communicated beyond the intestine indicates the ability of gut-derived microbial metabolites to act as a factor in the regulation of physiology.

The balance of all these activities of microbial metabolism in both production, exposure to the epithelium and recognition by the immune system and distribution to the system is important for the overall effect. There is a balance between beneficial metabolite profiles, maintaining integrity of barriers, immune tolerance, and controlled host defense reactions; while alterations in the metabolism of the microbes can lead to destabilization of these processes and induce inflammatory states. Thus, the composition and functional output of the microbiota are highly related to the fate of host homeostasis, where microbial metabolites dictate the beneficial or dysregulating immune response to host–microbiota interactions that lead to disease (Kim et al., 2024).

Immune homeostasis is a result of tightly coordinated relationships between the metabolism of microorganisms, epithelial barrier function, colonization resistance and local and systemic immunity. A good metabolite balance will help to build tolerance and good host defense, while imbalance and disruption of this network will damage barrier protection and will create a favorable environment for persistent inflammation and disease. The synergistic interplay of microbial metabolites with barrier integrity, mucosal immunity, colonization resistance and systemic communication is shown in Figure 2.

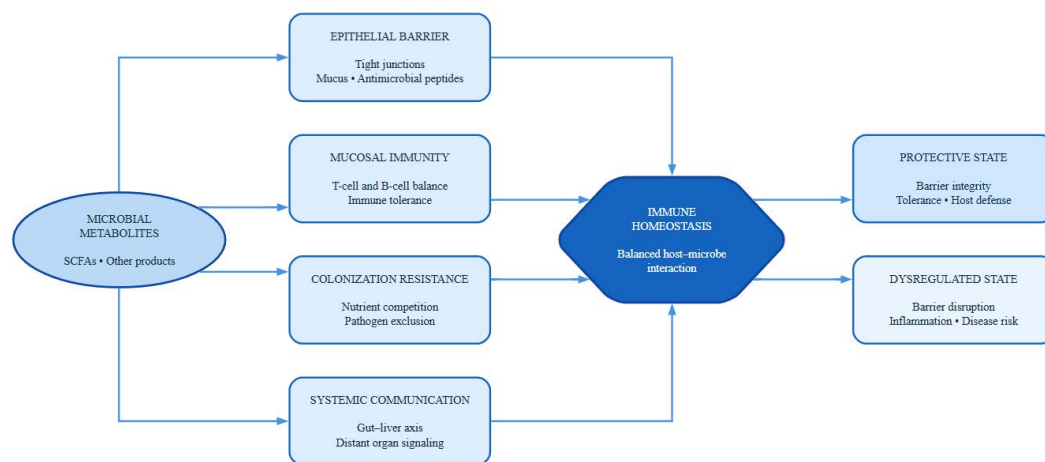


Figure 2. Microbial metabolite-mediated regulation of immune homeostasis and host defence

6. Microbial Metabolite Dysregulation in Disease Progression

Disturbances to the metabolic network of microbes can alter the normally homeostatic interactions between host and microbes to chronic inflammation. Dysbiosis can also affect the numbers, types and distribution of microbial metabolites, and also trigger oxidative stress, inflammatory activity and epigenetic abnormalities that can contribute to the onset and progression of metabolic diseases (Mostafavi Abdolmaleky & Zhou, 2024). This process is especially prominent in inflammatory bowel disease (IBD), where there are changes in the microbiota, as well as variations in the levels of certain SCFAs, bile acids, tryptophan metabolites and other bioactive metabolites. The changes may disrupt epithelial barrier function and affect mucosal immune regulation, thus aggravating intestinal inflammation (Hu et al., 2022).

Another context of impaired microbiota–immune axis communication that can lead to pathological immune activation is autoimmune diseases. Altered microbial populations and/or metabolism may disrupt immune tolerance, differentiation of lymphocytes, act as a trigger for inflammatory pathways, and affect barrier function, all of which can lead to conditions that favor autoreactive responses in susceptible individuals (Yurtseven et al., 2025). Other mechanisms may involve the production of microbial products or immune mediators that enter the systemic circulation, which may connect the dysbiosis of the gut with systemic autoimmune disorders (Mousa et al., 2022).

The significance of microbial cross-organ communication is also reflected in the occurrence of respiratory and allergic diseases. Microbial metabolites, barrier interactions and systemic inflammatory pathways are all pathways that can be impacted by changes in microbial community function and that have links to immune responses relevant to chronic respiratory diseases (Budden et al., 2019). In the gut–lung axis, dysbiosis and metabolic signaling changes may affect allergic sensitization, and the relationship between gut microbial disturbances and immunity in the lungs in allergic rhinitis has been established (Yang et al., 2025).

Microbiological metabolite profiles are also changed in metabolic and cardiovascular diseases. Dysbiosis can alter the production of short-chain fatty acids (SCFAs), trimethylamine metabolites, bile acid metabolites and other molecules involved in pathways of the vascular system, metabolism and inflammation, which are important to cardiovascular disease (Muttiah & Hanafiah, 2025). With obesity and obesity-related metabolic disorders, we can observe a change in the function of the intestinal microbial flora, which can lead to low-grade inflammation via disrupted barrier integrity and microbial products, as well as via metabolite-dependent immune signaling. This metabolic inflammation can then exacerbate insulin resistance and tissue dysfunction, establishing host metabolic and microbial ecological interactions (Tilg et al., 2020).

Metabolite dysregulation has other effects on the nervous system. Microbial metabolites may enter or communicate with the nervous system via circulation, immune, endocrine, and neural pathways, all of which can impact neuroinflammation, neuronal function and disease pathways. The altered SCFAs, microbial metabolites derived from tryptophan, and others have subsequently been linked to mechanisms that are important for several neurological diseases (Park & Kim, 2021). In severe infection, another type of metabolic disruption occurs in which immune activation and systemic physiological stress overwhelmingly reprogram host metabolism. These metabolic changes may become maladaptive in infections and sepsis and lead to organ dysfunction and immune dysfunction (Willmann & Moita, 2024).

The context-dependency of the activity of microbial metabolites is exemplified by cancer. Microbiota metabolites modulate antitumour immunity through various mechanisms, including alteration of T-cell function, myeloid-cell activity, immune checkpoints and the tumour microenvironment, and each metabolite can have different effects on immunity, either promoting or inhibiting immune control in a given context (Liu et al., 2025). Metabolite-mediated immune regulation may also play a role in tumour initiation and progression via inflammatory signaling, immune evasion and metabolic changes. The observed responses are likely not due to a broad immune response against tumour cells, but rather the result of the interplay between various microbial species, metabolites, tumour type, and host immunity and/or treatment exposure (Liu et al., 2023).

Disease-associated dysbiosis is most importantly functional when it changes the metabolic output of the microbes and/or alters microbial barrier, inflammatory, metabolic or immune-regulatory pathways. Metabolite effects occur in an inherent context-dependent manner: Across intestinal, autoimmune, respiratory, cardiometabolic, neurological, infectious and malignant diseases, the relationships between metabolites and causal immune responses are more informative than microbial composition alone. Comparisons of the main patterns of microbial metabolite dysregulation and their immune consequences are made in Table 3.

Table 3. Microbial metabolite dysregulation across major disease groups

Disease group	Main metabolic disturbance	Immune consequence	Disease relevance	Key references
Inflammatory bowel disease	Altered SCFAs, bile acids, indoles	Barrier failure; inflammation	Persistent intestinal inflammation	Hu et al., 2022
Autoimmune disease	Dysbiosis and altered metabolites	Loss of immune tolerance	Autoreactive responses	Yurtseven et al., 2025; Mousa et al., 2022
Respiratory/allergic disease	Gut–lung metabolic imbalance	Altered mucosal immunity	Chronic or allergic inflammation	Budden et al., 2019; Yang et al., 2025
Metabolic disease	Dysbiosis-driven metabolites	Low-grade inflammation	Insulin resistance	Tilg et al., 2020
Cardiovascular disease	SCFAs, TMA-related and bile acid changes	Vascular inflammation	Cardiometabolic dysfunction	Muttiah & Hanafiah, 2025
Neurological disease	Altered microbial metabolites	Neuroimmune dysregulation	Neuroinflammation	Park & Kim, 2021
Infection and sepsis	Systemic metabolic reprogramming	Immune dysfunction	Organ injury	Willmann & Moita, 2024
Cancer	Altered immunomodulatory metabolites	Immune escape or activation	Tumour progression	Liu et al., 2025; Liu et al., 2023

7. Therapeutic Translation and Future Research

The increasing knowledge of microbial metabolites and their role as regulators of immunity has led to potential opportunities for translating the knowledge of the microbiome into diagnostics and therapeutics. Functional changes associated with disease might be more directly reflected in disease-associated metabolite patterns than in taxonomic patterns. The combination of microbial signatures with circulating

or tissue metabolites might help to better classify disease, stratify risk and monitor treatment; however, large reproducibility issues will limit their use in routine practice for now, across populations and clinical settings (Hajjo et al., 2022).

One of the most interesting and promising fields for metabolite-guided intervention is cancer immunotherapy. Metabolites from microbiota can modulate antitumour immunity, immune-cell fitness, checkpoint activity, and treatment response, suggesting that defined metabolic signatures may be predictive or modulatory of responses to immunotherapeutic treatment. There are three types of translation strategies that can be used, such as restoring the production of beneficial metabolites, inhibiting the production of harmful metabolites, or targeting host pathways that are sensitive to metabolites in order to increase therapeutic efficacy (Perl et al., 2025).

A more general strategy for changing the metabolic output of the microbiome is through microbiome altering. Probiotics, prebiotics, synbiotics and postbiotics have the ability to affect the function of the microbial communities and the availability of metabolites, which in turn may influence the host metabolism and immune function. Unlike probiotics, postbiotics offer the potential for more targeted exposure to microbial bioactive products without the need for the live organisms themselves and come with the challenge of careful standardization of their composition, dosage, stability and mode of action (Li et al., 2021).

However, there are still significant obstacles to the development of bacterial metabolites as reliable immunomodulatory agents. A metabolite can have either a beneficial or adverse effect, depending on the concentration, tissue distribution, receptor expression, host genotype, stage of disease and microbial context. Other challenges include pharmacokinetics, off-target activity, inter-individual variability and inability to achieve physiologically relevant metabolite exposures in experimental and clinical settings (Saravanan et al., 2025).

Advancements in the future will rely on systems-level approaches that will connect microbial genes, metabolic pathways, host responses, and clinical phenotypes. Integrated metagenomics, transcriptomics, proteomics and metabolomics can supplement the identification of the taxa responsible for the production of metabolites and the definition of the mechanistic networks; however, in spite of significant advances, the comparability of cross-study results remains limited due to differences in sampling, analytical platforms, data integration and computational pathways (Daliri et al., 2021). Technological development is also needed to enhance the discovery and characterization, production and functional validation of microbial secondary metabolites having therapeutic potential (Singh et al., 2019). The steps from metabolite discovery to clinical biomarkers, therapeutic intervention, technological validation, and precision microbiome therapy are highlighted in Figure 3.

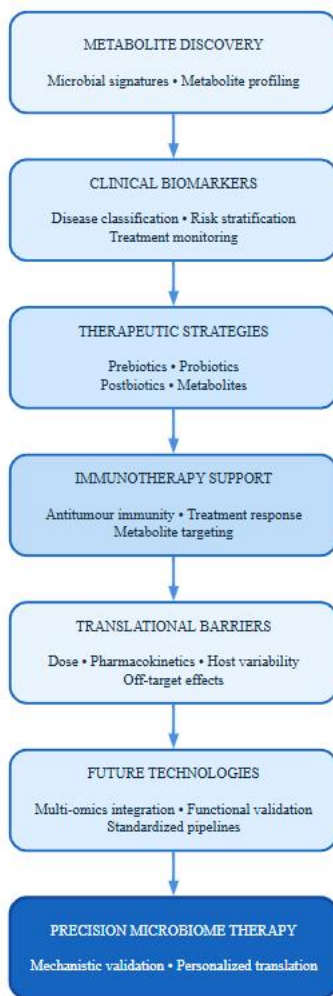


Figure 3. Translational roadmap for microbial metabolite-based diagnostics, therapeutics, and precision immunomodulation

Future work needs to then go beyond description to testable and causal frameworks. Longitudinal human studies, controlled dietary or microbiome interventions and organoid systems, gnotobiotic models and spatial or single-cell analyses will be especially useful for determining when and where particular metabolites are at work. The precision aspect of strategies needs to take into consideration host genetic variation, baseline microbiota, dietary and medication exposures, as well as disease phenotype to avoid making the assumption that all individuals will respond to the same strategies. The most promising translation opportunities are the use of microbial metabolites as functional biomarkers, therapeutic agents and modulators of treatment response. Progress in the clinic will rely on the causal demonstration, context-dependent standardization of multi-omics, precise identification of metabolites and personalized interventions based on biological context.

8. Conclusion

In addition to microbial composition, microbial metabolites represent a large functional aspect of the microbial communities that shape host immunity. These short-chain fatty acids, tryptophan metabolites,

bile acids, polyamines, vitamins, and microbial lipids interact in a complex fashion, impacting epithelial integrity via receptor-mediated and epigenetic pathways, as well as innate and adaptive immune cell function through inflammatory and immunometabolic pathways. Such interactions play a key role in sustaining mucosal tolerance, colonization resistance, systemic immune balance and effective host defense. Disruption of this metabolic balance can affect barrier function, signal inflammatory processes and program immune cells, which can lead to disease processes in the intestine, autoimmune diseases, respiratory systems, cardiometabolic diseases, neurological diseases, infectious diseases and even malignant diseases. Importantly, metabolite effects are dependent on the context and can be dose-, tissue-, receptor expression-, and host physiology-dependent. The potential impact of this field is to go from association to clinically testable and causal mechanisms. Rigorous validation with standardized multi-omics and focus on interindividual variability is essential for the application of promising metabolomics-related biomarker approaches, postbiotics, receptor-targeted approaches, and modulation of response to treatment. Moving forward towards mechanistic precision and personalized microbiome-based immunomodulation should be a priority.

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