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Microbiota, chronic inflammation, and health: The promise of inflammatome and inflammatomics for precision medicine and health care

Huan Zhang[#], Bing Jun Yang Lee[#], Tong Wang[#], Xuesong Xiang[#], Yafang Tan, Yanping Han, Yujing Bi, Fachao Zhi, Xin Wang, Fang He, Seppo J. Salminen[*], Baoli Zhu[*], Ruifu Yang[*]

[#]These authors contributed equally to this work.
*Correspondence: sepsal@utu.fi (S.J.S.); zhubaoli@im.ac.cn (B.Z.); ruifuyang@gmail.com (R.Y.)
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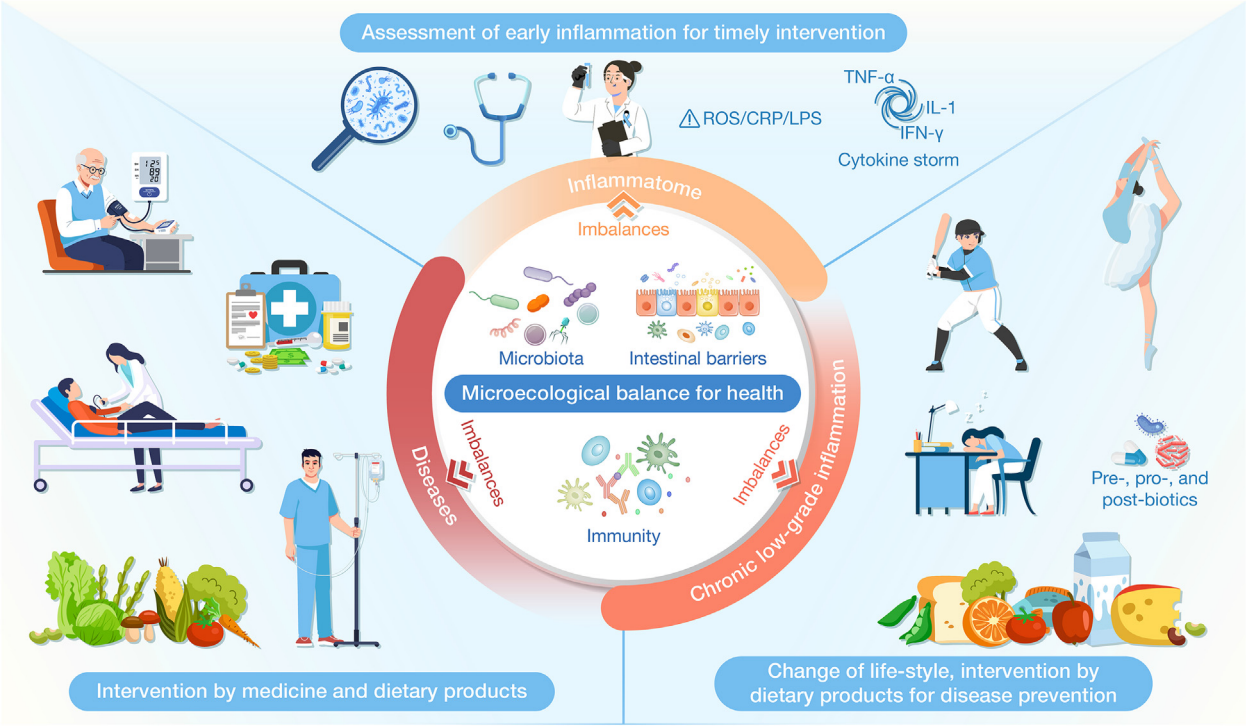
GRAPHICAL ABSTRACT



HIGHLIGHTS

- **Proposed “inflammatome” (holistic inflammation network) & “inflammatomics” (decoding dysbiosis-driven chronic inflammation).**
- **Microbiota–immune crosstalk modulates inflammation and disease progression, informing targeted therapeutic strategies.**
- **Chronic inflammation underlies metabolic/neurodegenerative disorders, revealing shared pathomechanisms.**
- **Inflammatomics enables precision medicine *via* early detection, personalized interventions, and predictive biomarkers.**

REVIEW

Microbiota, chronic inflammation, and health: The promise of inflammatome and inflammatomics for precision medicine and health care

Huan Zhang[1,2,#], Bing Jun Yang Lee[3,#], Tong Wang[2,#], Xuesong Xiang[4,#], Yafang Tan[2], Yanping Han[2], Yujing Bi[2], Fachao Zhi[5], Xin Wang[6], Fang He[7], Seppo J. Salminen[8,*], Baoli Zhu[9,10,*], Ruifu Yang[1,2,*]

[1]School of Public Health, Hebei Medical University, Hebei, China
[2]State Key Laboratory of Pathogen and Biosecurity, Academy of Military Medical Sciences, Beijing, China
[3]Hong Kong Yanstone Preventive Science Co., Limited, Hong Kong, China
[4]National Institute of Nutrition and Health, China Center for Disease Control, Beijing, China
[5]Guangdong Provincial Key Laboratory of Gastroenterology, Department of Gastroenterology, Institute of Gastroenterology of Guangdong Province, Nanfang Hospital, Southern Medical University, Guangdong, China
[6]State Key Laboratory for Managing Biotic and Chemical Threats to the Quality and Safety of Agro-products & Food Sciences Institute, Zhejiang Academy of Agricultural Sciences, Zhejiang, China
[7]West China School of Public Health and West China Fourth Hospital and Healthy Food Evaluation Research Center, Sichuan University, Sichuan, China
[8]Functional Foods Forum, Faculty of Medicine, Itäinen Pitkäkatu 4A, FI-20014, University of Turku, Southwest Finland, Finland
[9]Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China
[10]University of Chinese Academy of Sciences, Beijing, China
[#]These authors contributed equally to this work.
*Correspondence: sepsal@utu.fi (S.J.S.); zhubaoli@im.ac.cn (B.Z.); ruifuyang@gmail.com (R.Y.)
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ABSTRACT

The terms "inflammatome" (holistic inflammation networks) and "inflammatomics" (a novel omics field) were proposed to decode dysbiosis-driven chronic inflammation and its disease links. Inflammatomics explores microbiota–immune crosstalk, particularly innate immune interactions, revealing how dysregulated microbial communities trigger chronic inflammation underlying disorders like inflammatory bowel disease, metabolic diseases, and neurodegeneration. This discipline transcends traditional inflammation paradigms by dissecting molecular pathways connecting dysbiosis to systemic inflammation, enabling early detection and precision interventions. It integrates evolutionary perspectives on host–microbe interactions, emphasizing the human body as a stress-sensitive "organ". Challenges include standardizing inflammatome profiling, translating findings into clinical tools, and advancing multiomics technologies. By bridging microbial ecology, immunology, and systems medicine, inflammatomics holds a transformative potential to shift health care from reactive treatment to proactive, personalized prevention, targeting disease origins shaped by chronic inflammatome dysregulation.

KEYWORDS inflammatome; inflammatomics; dysbiosis; chronic inflammation; healthcare; medicine

INTRODUCTION

The human microbiota, comprising trillions of microorganisms inhabiting various niches within our body, plays an integral role in maintaining homeostasis and influencing specific physiological processes [1–3]. The expansive domain of minuscule organisms encompasses a diverse range of life forms including bacteria, viruses, fungi, protozoa, archaea, and other microorganisms [4]. It has been established that there are various communication pathways between the gut microbiome and other bodily organs, including neural, endocrine, and immune systems, which is called the "gut–X axis" defining the interplay between microbiota, gut, and other tissues or organs, like gut–liver axis and gut–brain axis. The emergence of the "gut–X axis" theory has made a revolutionary contribution to modern medicine, providing us with an opportunity to revolutionize and complement existing medical theories from the perspective of the "microbiome–gut–X axis" theory [5,6].

This makes us redefine human being as a superorganism or a holobiont [7,8], which comprises the human body, mind, and microbiome. The balance between these three players determines our health and diseases. Dysbiosis, a state marked by microbial imbalance or maladaptation within this intricate ecosystem, can incite a cascade of events leading to chronic inflammation [9]. From an ecological viewpoint, understanding that imbalances in gut microbiota can contribute to various diseases requires a paradigm shift to pathobionts from the traditional perception of a single microorganism—like bacteria, viruses, fungi, or parasites—solely causing a particular disease, the traditional "pathogen" concept. The perspective of pathobionts [10–12] refers to a collection of microorganisms causing dysbiosis that forms the potential underlying cause of diseases such as diabetes, chronic diseases, cardiovascular and cerebrovascular diseases, etc. Dysbiosis of gut microbiota may cause neuroinflammation, which is related to eating disorders, such as anorexia nervosa, binge eating disorder, and bulimia nervosa, indicating that adjusting the gut microbiota could be a really good way to treat these problems [13]. Acknowledging the pathobiont concept marks a significant stride forward in the realm of medicine. A recent study identifies a core microbiome signature that represents a stable, enduring relationship among gut bacteria across specific conditions, offering a holistic health indicator and potential target for enhancing human health [14]. Understanding the complex interplay between microbiota and health has evolved significantly [15,16], leading to the emergence of a critical concept here we proposed as inflammatomics.

Inflammatomics, inflammation omics, is an emerging omics system along with the development of medicine and life science. It is a science that studies the origins and causes of inflammation, the laws of change, and intervention countermeasures to promote health and prevent diseases. Inflammatomics targets responses to different types of infections and other inflammation-related diseases over millions of years of evolution. It is one transformative discipline, which unveils the molecular underpinnings of inflammatome or inflammatomic caused by persistent inflammation triggered by dysregulated microbial communities within the human body. Like other omics fields such as nutrigenomics, immunomics, genomics, proteomics, metabolomics, etc., inflammation omics is an important branch in the field of medicine and life science, serving as an essential tool for us to understand health and overcome diseases. Through inflammatomics research, the body's inflammatory state, named the inflammatome, is revealed from multiple perspectives. As can be seen from Figure 1, the sources of the inflammatome are multifaceted.

Inflammatome or inflammatomics refers to all the inflammation networks in an organism. The inflammation has two states, acute inflammation and the chronic one. Acute inflammation in inflammation omics is the primary defensive response of the humans or animals to infections caused by pathogenic microorganisms. Since the invention of vaccination by Edward Jenner in 1796 [17] and the discovery of the first antibiotic penicillin by Alexander Fleming in 1928 [18], we have been armed with the primary medical methods to struggle against acute inflammation and prevent infectious diseases, significantly increasing the average lifespan of humans. Chronic inflammation in inflammation omics is the inducement and root cause of many chronic non-communicable diseases. The breakthrough in chronic inflammation prevention and control system should involve the systemic quantitative evaluation of health and pre-disease state, as well as the evidence-based intervention techniques and products for preventing and reversing chronic diseases.

Basic and applied research in inflammation omics, as well as its crossover and infiltration with other omics fields in translational applications, will generate numerous research areas, such as the microbiological, immunological, pathological, genetic, and chemical bases of inflammation; the pharmacological, dietary, and nutritional bases of inflammation; the relationship between inflammation and endocrinology and neurology; the association between circadian rhythms, barrier integrity, and the occurrence, development, and resolution of inflammation; and the research on the relationship between inflammation and the occurrence and development of diseases (such as chronic diseases, tumors, neurodegenerative diseases, etc.). These will play an indispensable role in maintaining and promoting human health and preventing as well as treating diseases.

INFLAMMATOME AND INFLAMMATOMICS

Inflammatome, a Result of Dysbiosis

The balance among microbiota indicates the humans' health [14], and the interrupted balance, resulting in dysbiosis, will be associated with persistent chronic inflammation and potential foundation of chronic diseases [19]. As shown in Figure 1, dysbiotic chronic inflammation can be caused by a complex mechanism, involving interaction between microbiota and host. Taking the intestine as an example, the four barriers, biological, chemical, physical, and immune barriers, play critical roles in the development of inflammatome [20,21]. Except for the endogenous interactions, the balance between intestinal barriers is also impacted by exogenous factors, such as antibiotics and unhealthy diets or microbial infections [22,23]. This chronic low-grade inflammation has been described in the literature as metaflammation [24], which is proposed to originate from the evolutionarily conserved nutrition-sensing and immune signaling pathways. Metaflammation may lead to tissue damage, organ dysfunction, and the perpetuation of pathological conditions [24,25]. For studying inflammatome steps into this realm, inflammatomics aims not only to understand the origins of this chronic inflammation but also to delineate the signaling cascades and cellular interactions perpetuating it, especially finding the low-grade chronic inflammation that current medical tests cannot detect in the pre-disease state. Such comprehensive insights are crucial in redefining disease management strategies beyond mere symptom alleviation. Inflammatome places a greater emphasis on investigating the origins of low-grade chronic inflammation before symptoms appear and uncovering the

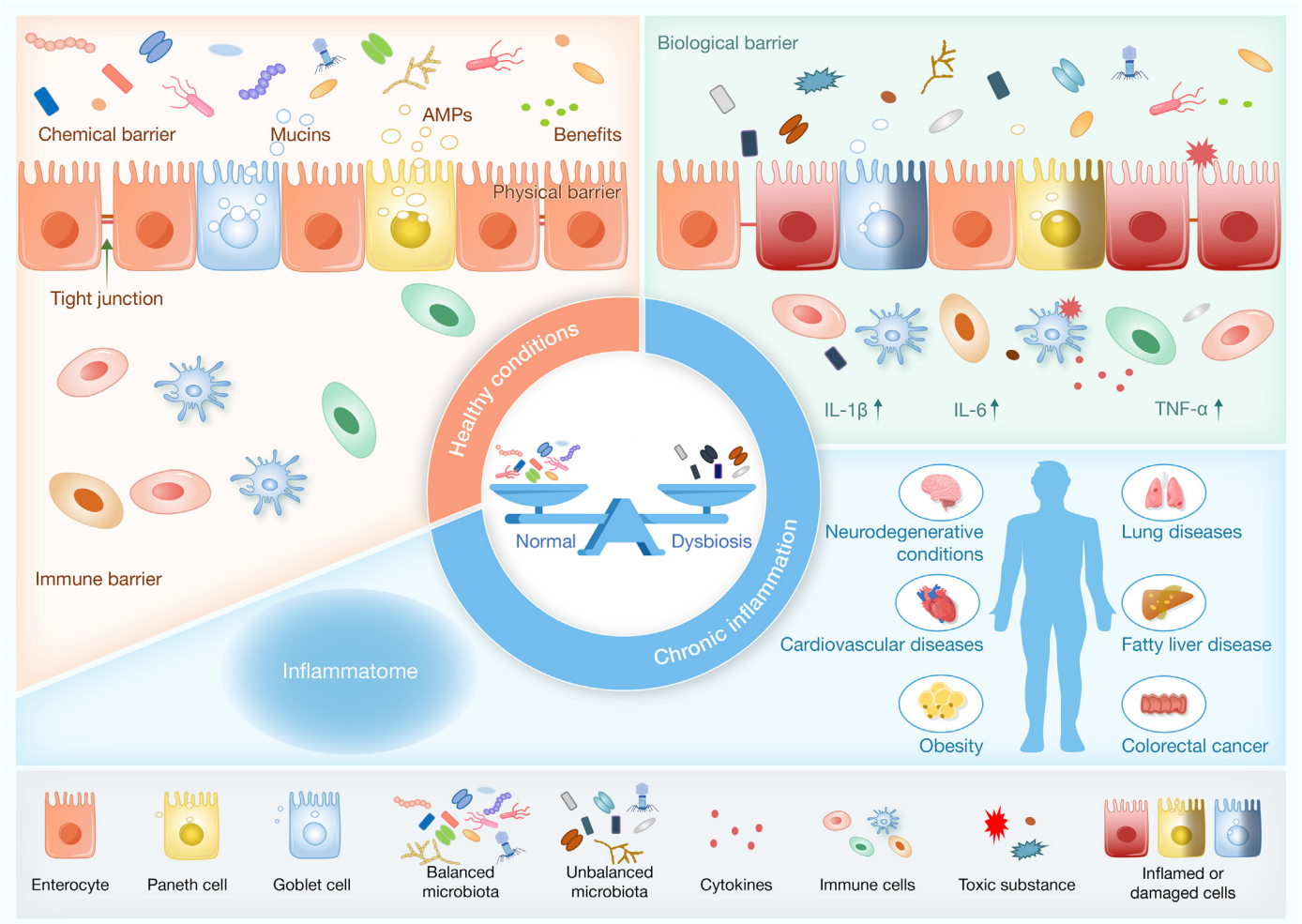

Figure 1. The origin of inflammatome and its impact on health
The intestinal barrier consists of the following four barriers: the physical barrier formed by tight junctions between intestinal epithelial cells, the chemical barrier composed of AMPs, mucins, and other benefits, the biological barrier made up of the microbiota in the intestinal lumen, and the immune barrier located beneath the intestinal wall. The balance of these barrier functions is crucial for maintaining a healthy gut. However, when factors such as an unhealthy diet and medication lead to an imbalance in intestinal microecology, it can result in the disruption of these barriers, which in turn triggers the onset of chronic inflammation. If chronic inflammation is not timely controlled, this chronic low-grade inflammatome can lead to the development of various diseases, including obesity, diabetes, fatty liver, cardiovascular diseases, cerebrovascular diseases, pulmonary diseases, and even cancers. Abbreviations: AMPs, antimicrobial peptides; IL-β, interleukin-β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

fundamental factors to induce it for early sensitive detection and for designing and implementing intervention strategies for restoring and maintaining a healthy state.

Inflammatomics, Omics Research Focusing on Revealing Mechanisms Behind Inflammatome

In this review, the discussion on inflammatomics specifically refers to the molecular basis of chronic, low-grade inflammatory responses in the body caused by the imbalance of the microbiota. It involves a series of reactions following the disequilibrium of homeostasis between the human microbiome, the immune system, the physical barrier of epithelial cells, and the chemical barrier of the mucus layer. The long-term presence of dysbiosis, destruction of the mucus layer, impairment of the physical barrier, and an overactive immune response can lead to chronic inflammation in local areas of the body, such as the intestines, ultimately leading to chronic health degeneration and the onset and progression of chronic diseases. From another perspective, we can also define inflammatomics as an integrative and multidisciplinary discipline encompassing the comprehensive study of dysbiosis-induced chronic inflammation at a molecular, immunological, and pathological level within the human body. It involves the exploration of multi-omics data, host–microbiota interactions, and inflammatory pathways to unravel the intricate connections between dysregulated microbial communities and sustained low-grade chronic inflammation across various diseases [16]. The significance of inflammatomics lies in its capacity to unravel the intricate connections between dysbiosis and chronic inflammation, providing invaluable insights into disease-triggering mechanisms that were previously elusive. By exploring the molecular pathways through which dysbiosis triggers and perpetuates chronic inflammation, this concept offers a transformative perspective on the etiology and progression of various diseases [26,27]. It provides a crucial perspective for

understanding the underlying processes of health and illness, with the potential to revolutionize medicinal and healthcare strategies. From metabolic disorders like obesity and type 2 diabetes (T2D) to inflammatory bowel diseases (IBDs) and even neurodegenerative conditions [28], dysbiosis-induced persistent chronic inflammation has emerged as a common denominator, often initiating and fueling disease progression (Figure 1). Recent findings clearly demonstrate the association of gut microbiota dysbiosis with the development of T2D [29].

Inflammatomics for Early Defining of Pre-disease State

The research on inflammatome differs from the traditional disease research models. Traditional research aims to find markers of a specific disease and develop new strategies for diagnosis and treatment. However, the research on inflammatome focuses on a predisease state or early state of the disease. Taking the assessment of intestinal microecology as an example, it needs to evaluate these functions from the ecological perspective of the complex interactions among the physical, chemical, immune, and biological barriers. Since it is a low-grade persistent chronic inflammatory state before or in the early stage of disease, we need more systematic methods and more sensitive tools to assess and discover the spectrum of markers for different predisease states, which can be used for early detection and diagnosis of diseases or health issues. Meanwhile, based on the research on mechanism of the occurrence and development of inflammatome and diseases, we also need to develop corresponding efficient intervention products and strategies to restore intestinal microecological balance for preventing and treating the occurrence and development of diseases. Therefore, inflammatomics not only focuses on the diagnosis and treatment of diseases but more importantly, it evaluates health status, detects chronic low-grade inflammation problems early, intervenes promptly to restore health status, maintains the balance of intestinal microecology, and maintains physical health.

Studies using inflammatomics have been instrumental in elucidating the mechanistic underpinnings of dysbiosis-induced chronic inflammation in disease pathogenesis. For instance, research utilizing metagenomic and metabolomics analyses has identified specific dysbiotic signatures and microbial metabolites associated with inflammatory responses in various diseases [30,31]. These studies highlight the potential of inflammatomics to unravel disease-specific microbial patterns and inflammatory pathways, providing insights into disease initiation and progression.

Moreover, advancements in high-throughput sequencing technologies have enabled the identification of microbial biomarkers and inflammatory signatures characteristic of different disease states. By leveraging *de novo* assembled high-quality metagenome-assembled genomes (HQMAGs) and applying a 1% average nucleotide identity (ANI) threshold for differentiation, Wu et al. achieved near-strain-level resolution, enhancing insights into the functions of health-associated microbes, paving the way for more detailed identification and comprehension of microbial functions in both health and pathology [14]. The authors examined metagenomic data from a fiber-rich diet intervention in T2D, along with 26 case-control investigations spanning 15 illnesses and pinpointed a collection of genomes that consistently co-occurred within networks affected by dietary changes and diseases. They defined a "two competing guilds" framework, where one guild is dedicated to fiber fermentation and butyrate synthesis, while the other is marked by pathogenicity and antibiotic resilience. Recent insights into the microbiome makeup at locations of inflammatory dysbiosis have sparked considerable interest in a range of previously overlooked bacteria, particularly among fastidious obligate anaerobes. *Parvimonas micra* stands out as a prime case of such a microbe, and it is frequently detected in high numbers at numerous mucosal sites afflicted by either chronic or acute inflammatory conditions [32,33]. It has been suggested as a potential biomarker for various cancers because it thrives in environments of active inflammation and tissue damage.

Because nucleic acid sequencing and subsequent bioinformatics analysis require a relatively long period of time, the development of rapid assessment methods, e.g., those based on polymerase chain reaction (PCR), is urgently needed, as reported recently in the real-time quantitative PCR (RT-qPCR) detection technology based on the core microbiome [34]. These biomarkers, derived from inflammatomics-driven analyses, hold promise in early detection of diseases, defining prognostic factors, and monitoring of therapeutic responses. They serve as valuable tools for stratifying patients based on their inflammatory profiles influenced by dysbiosis, facilitating tailored interventions and precision medicine and healthcare approaches.

Translational Potential of Inflammatomics

The healthcare landscape stands poised for a transformative shift as inflammatomics offers a promising avenue for precision health care and medicine [35]. By unraveling the intricate web of dysbiosis-induced inflammation in individual patients, clinicians can potentially tailor interventions and therapies that address the root cause of the disease rather than merely managing its symptoms [36]. This personalized approach, based on the patient's unique inflammatory profile influenced by dysbiosis, holds the promise of more effective and targeted treatments, potentially minimizing adverse effects and optimizing therapeutic outcomes.

Moreover, the implications of inflammatomics extend beyond the realm of individualized medicine. Understanding the role of dysbiosis-induced chronic inflammation in disease pathogenesis opens doors to preventive strategies at a population level [35,37]. By identifying individuals at risk based on their inflammatory profiles influenced by dysbiosis, interventions aimed at modulating the microbiota or quelling chronic inflammation could potentially curb the onset or progression of various diseases [38,39]. This preventive paradigm shift could significantly alleviate the burden on healthcare systems globally by reducing the incidence and severity of chronic conditions.

Inflammatomics stands at the frontier of biomedical research, poised to redefine our understanding of disease processes influenced by dysbiosis-induced chronic inflammation [40,41]. Its implications extend far beyond theoretical realms, holding the potential to revolutionize clinical practice, improve patient outcomes, and pave the way for a proactive approach to healthcare. As research in this field progresses, the promise

of inflammatomics to unveil the hidden connections between dysbiosis and chronic inflammation ignites hope for a future where diseases can be understood, managed, and even prevented at their core.

MICROBIOTA AND ITS ROLE IN IMMUNITY

Composition and Function of the Microbiota

Composition of microbiota

The human body is home to trillions of microbes, collectively known as the microbiota with remarkable diversity, which play a crucial role in maintaining health [30]. The gut microbiota is a complex ecosystem that is populated by trillions of bacteria, fungi, viruses, and other microorganisms, and the microbial composition is influenced by various factors, including genetics, diet, lifestyle, and environmental exposures. The gut microbiota is diverse and highly dynamic. Within the host, the composition of the microbiota and its evolution driven by natural selection are influenced by ecological interactions of competition or cooperation [42]. This intra-host evolution may be related to the occurrence of diseases; it is crucial to better understand the rules of intra-host evolution of microbial communities, as well as how these rules depend on the biological characteristics of each microorganism, which is essential for developing more effective microbiome therapeutic methods.

Physiological functions of microbiota

The microecosystem contributes to various physiological processes, including nutrient metabolism, defense against invading pathogens, maintaining the intestinal barrier, and modulating the immune system [43]. For nutrient metabolism, the gut microbiota assists in breaking down dietary components that the human body cannot digest directly, such as cellulose and other complex carbohydrates, producing beneficial metabolites such as short-chain fatty acids (SCFAs). These metabolites not only provide energy to intestinal cells but also regulate fat metabolism, cholesterol homeostasis, and vitamin synthesis, crucial for maintaining human health. The human intestinal microbiome is crucial in defense against the establishment of harmful pathogens within the host. The increased diversity of the microbial community possesses the combined capacity of the resistant communities to deplete nutrients that are also required by the pathogens [44]. The biological barrier formed by microbiota closely interacts with the intestinal mucosa to maintain the stability of the gut environment. In addition to competing for nutrients, this barrier also competes for attachment sites for the prevention of growth and reproduction of harmful microorganisms. Furthermore, the microbiota produces antimicrobial substances [45], such as bacteriocins and antimicrobial peptides (AMPs), that directly kill or inhibit the activity of pathogenic bacteria. The gut microbiota significantly impacts the development and function of the immune system [46]. It can stimulate the development and activation of intestinal lymphoid tissue, promoting the proliferation and differentiation of immune cells. Furthermore, the microbiota modulates the activity and function of immune cells, such as regulating the balance of T-cell subsets and promoting antibody production, thereby enhancing the host's resistance to infections. A novel link between vitamin D, gut microbiota, and immune responses to tumors was reported [47]. Vitamin D may regulate the composition and activity of microbiota regulating anti-tumor immunity. The level of vitamin D is also a potential determinant of anti-tumor immunity and immunotherapy success, with extensive clinical and public health implications.

Functions of microbiota metabolites

Extensive gut microbiota-derived metabolites have been identified to date. They can be broadly categorized into three distinct groups, differentiated by their source and the process of synthesis [48]: firstly, those synthesized by intestinal microbes from the nutrients found in our diet; secondly, those initially produced by the host organism and subsequently altered by the gut microbiota; and thirdly, those capable of being remanufactured by the gut bacteria themselves.

Digestive enzymes from the gut microbiota break down complex carbohydrates in food and mucins into monosaccharides with five or six carbon atoms. These sugars are then further degraded through the pentose phosphate or glycolytic pathways to yield pyruvate. Pyruvate, along with its precursor phosphoenolpyruvate, undergoes multiple metabolic conversions, ultimately leading to the generation of SCFAs. Studies have indicated that the Bacteroidetes, a group of bacteria in the gut microbiota, enhance insulin sensitivity by metabolizing carbohydrates, especially simple sugars like glucose, fructose, galactose, mannose, xylose, and arabinose [49].

Metabolites produced by the gut microbiota, including SCFAs, aromatic amino acids and their derivatives, polyamines, bile acids, etc., regulate the differentiation and function of adaptive and innate immune cells [50]. They also play potential roles in various systemic diseases.

SCFAs, especially butyrate, promote the differentiation of regulatory T cells (Tregs) by inhibiting histone deacetylases and play a key role in anti-inflammatory responses [50]. SCFAs exert their influence on host cells through various mechanisms, such as signal transduction *via* G protein-coupled receptors (GPCR), the acetylation of histones and transcription factors, and the function of butyrate as a ligand for transcription factors, thereby modulating cellular functions and gene expression [51]. Metabolites of aromatic amino acids, such as tryptophan-derived indole compounds, act as ligands for the aryl hydrocarbon receptor (AhR), affecting the activation of group 3 innate lymphoid cells (ILC3s) and T helper 17 (Th17) cells, thereby participating in the maintenance of intestinal immune homeostasis [50]. The gut microbiota can metabolize and modify bile acids [52]. They act *via* the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor TGR5 [50,53], impacting energy balance, thyroid hormone activity, and immune modulation [54], promoting health. Two bacteria, *Gordonibacter pamelaeae* and *Eggerthella lenta*, in the human gut have been discovered to have the ability to convert steroids into bile, playing a positive role in promoting the production of progestins during pregnancy [55]. Gut microbes alter lipids, key for immune and metabolic regulation, influencing chronic diseases and cellular signaling [56].

Branched-chain amino acids (BCAAs) signal a higher T2D risk; gut microbes affect their levels, impacting insulin resistance. Certain bacteria boost BCAA synthesis, while others hinder uptake and catabolism. In heart failure, BCAA buildup can cause oxidative stress and mitochondrial dysfunction [54].

Parabacteroides merdae may mitigate cardiovascular harm by enhancing BCAA catabolism [57]. The tryptophanase of gut microbiota metabolizes tryptophan into indole, which then enters the host's circulatory system. In the liver, it is converted to indoxyl sulfate and subsequently excreted by the kidneys [53]. High levels of indoxyl sulfate exhibit nephrotoxicity, and many of these compounds act as ligands for the AhR. Polyamines like spermine and spermidine, synthesized by the host and microbiota or from dietary intake, are key in biological processes. Gut microbes mainly produce polyamines through the transamination action of catalytic enzymes, breaking down ingested amino acids (especially arginine) and are extensively involved in physiological and pathological processes within organisms [58].

B vitamins are obtained from both diet and synthesis by the gut microbiota, with the production of folate (vitamin B9) by colonic microbes exceeding dietary intake. Infant gut microbiota is rich in genes for *de novo* synthesis of folate, while the microbiota of adults is abundant in genes related to the metabolism of folate and its reduced form, tetrahydrofolate. Therefore, the gut microbiota is an important source of essential vitamins and may offer new strategies for the treatment of vitamin deficiencies, especially those not related to diet [53].

Choline, from diet or synthesis, is converted by gut microbes to trimethylamine (TMA), metabolized to trimethylamine N-oxide (TMAO) in the liver, linked to atherosclerosis and cardiac events [53], and influences tumor immunity [59].

Gut microbes make neurotransmitter precursors and synthesize them from diet, affecting brain function, and are linked to neurological disorders. Neurotransmitters can enter blood, cross the blood-brain barrier, and influence sensory signals *via* the vagus nerve. Changes in the synthesis of neurotransmitters/precursors regulated by the gut microbiota may lead to alterations in brain function and affect neurological disorders such as Alzheimer's disease, Parkinson's disease, autism, and schizophrenia. A recent study found that the neurotransmitter tyramine produced by the gut symbiotic bacterium *Providencia* can manipulate the host's sensory decision-making behavior by bypassing the host's tyramine biosynthetic pathway [60].

Microecosystem: A Fragile and Adjustable Organ

Human microbiota has been considered as a neglected organ that plays an indispensable role in health maintenance and disease development [61]. The microbiota has close interaction with the host, constituting a microecological system [62]. This microecosystem is complex and should be treated as a changeable organ like the liver, gut, kidney, heart, lungs etc. The composition and interactive relationship with the host of this organ are easily impacted by diets, antibiotics, lifestyle, etc. [63]. Microbes in food contribute to the composition of the microbiome in adults [64,65] and hence influence the host metabolism. Gut microbiome, nutrients, and the immune system interact with each other closely to determine human health and disease (Figure 2) [66]. Because the dynamic balance of the microecosystem is an adaptive process to different environmental stimulants, we here propose the microecosystem as a fragile organ for alerting us to pay attention to it, doing our best to understand the complex mechanisms of its balance, and keeping it unharmed by microbiota-directed foods.

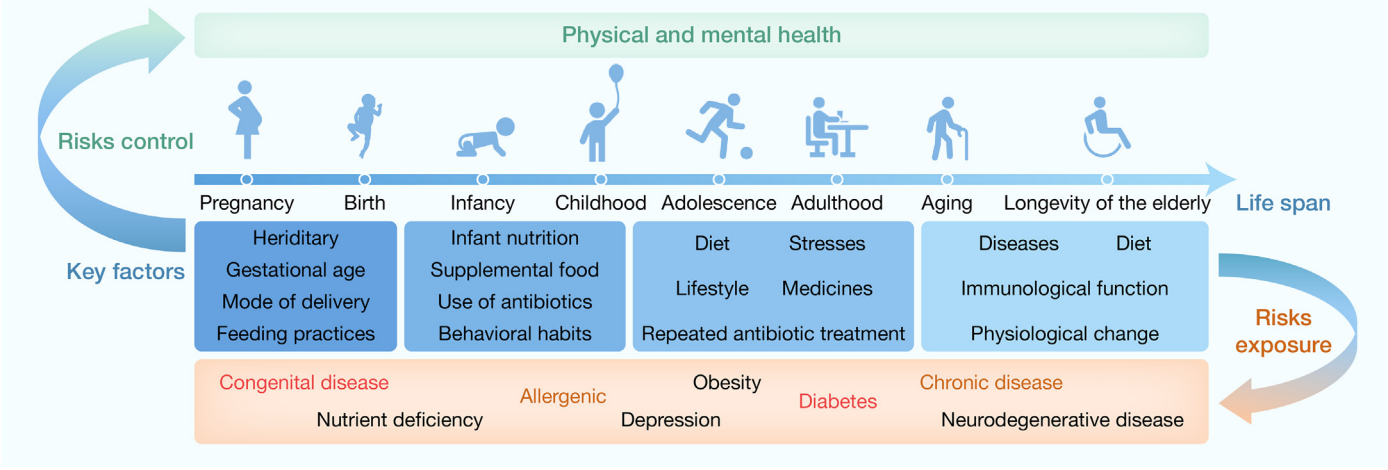

Figure 2. Factors contributing to dysbiosis and inflammation throughout the life span and their impact on health
The figure illustrates the various stages of the human life cycle and the factors that influence physical and mental health at each stage. The key factors are illustrated at different stages of life, including pregnancy (factors such as genetics, maternal age, delivery methods, and feeding habits), infancy (factors like infant nutrition, complementary foods, antibiotic use, and behavior), childhood (factors including diet, lifestyle, medication, and repeated antibiotic use), adolescence (stress as a key factor), adulthood (diet as a key factor), aging (factors such as diseases, immune function, and physiological changes), and longevity of the elderly (diet as a key factor). All these factors impact the balance of microbiota–host interaction. The red arrow indicates the risk exposure, showing that risk factors can lead to dysbiosis and health problems; it gives rise to distinct health challenges at various stages of life: congenital disorders during pregnancy and childbirth, nutritional deficiencies in infancy, allergies in childhood, obesity during adolescence, depression in adulthood, diabetes as one ages, and chronic as well as neurodegenerative diseases in the later years of life. The green arrow shows that risks control can improve health outcomes.

Interactions with the Immune System

Role in development of immune tolerance

The gut microbiota plays a key role in the early development of immune tolerance and balance. The immunity of both the fetus in the uterus and the newborn are biased by T helper type 2 (Th2); while the early development of the immune system is mainly innate, the inhabitant microbiota gradually matures after birth and plays a critical role in maturation of T helper type 1 (Th1)/Th2 cells' balance [67]. In the neonatal gut, gut microbes enhance the availability of serotonin (5-hydroxytryptamine [5-HT]) that can modulate T-cell metabolism by elevating the levels of intracellular indole-3-acetaldehyde, thereby inhibiting the activation of the mammalian target of rapamycin (mTOR) pathway. This modulation fosters the emergence of Tregs and reduces the activation of helper T cells within the neonatal small intestine [68]. This is instrumental in establishing long-term immune tolerance toward dietary proteins and commensal gut bacteria. Certain gut bacteria engage in two-way communication with the host's serotonergic system, thereby enhancing their survival and adaptation within the intestinal environment.

Role in maturation of T helper 17

The gut microbiota is closely associated with the maturation of Th17. The signaling pathway involving interleukin-17 (IL-17) and its receptor (IL-17R) is vital for the regulation of the body's mucosal defenses against various pathogens. Among the commensal bacteria, segmented filamentous bacteria (SFB) play a pivotal role in the maturation of Th17 cells within the gastrointestinal tract [69]. The interleukin-23 (IL-23) signaling pathway plays a crucial role in modulating the population of SFB and the integrity of the mucosal barrier in mature mice [69]. When the IL-17R signaling in the intestinal lining is compromised, the production of α-defensins, polymeric immunoglobulin receptor (Pigr), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (Nox1) is decreased, leading to an imbalance in the SFB population [70]. RORγt$^+$ Th17 cells play a dual role in the body, being crucial for the defense of mucosal surfaces while also being implicated in the development of autoimmune conditions. They accumulate in the intestinal tract as a reaction to the presence of the microbiota and are responsible for the production of IL-17 cytokines. Among the gut microbiota, the colonization of SFB can activate RORγt$^+$ T cells in the mesenteric lymph nodes. The production of IL-17A is particularly strong in the ileum, where SFB interacts closely with the epithelial layer, triggering the production of serum amyloid A proteins 1 and 2 (SAA1/2). These proteins, in turn, enhance the local expression of IL-17A in RORγt$^+$ T cells [71]. An SFB-dependent role of ILC3s, which release interleukin-22 (IL-22) that stimulates the production of SAA by the epithelium in a signal transducer and activator of transcription 3 (STAT3) pathway-dependent process [71]. IL-22 signaling in Paneth cells plays a regulatory role in the composition of the intestinal commensal bacteria and in the immune response mediated by IL-17A, which is influenced by the microbiota [72]. Recently, the engineered miniproteins that effectively target interleukin-23 receptor (IL-23R) and IL-17 robustly inhibit cellular signaling *in vitro* and are remarkably stable, which can successfully penetrate the gut epithelial barrier to engage a therapeutic target, representing an exciting new avenue for the development of orally administered biological therapies [73].

Interactions with the host's innate immune receptors

The microbiota activates innate immune cells by stimulating pattern-recognition receptors (PRRs). The receptors of innate immune cells play crucial roles in triggering and orchestrating immune responses against various pathogens and foreign substances; they also play critical roles in interactions between gut microbiota and the immune system. The identification of innate immune sensors, known as PRRs, has significantly reshaped our comprehension of innate immunity. PRRs recognize conserved molecular patterns commonly found in pathogens, such as bacterial lipopolysaccharides (LPSs) and fungal β-glucans [74]. PRRs include toll-like receptors (TLRs) (TLR1–13), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (NOD1 and NOD2), nucleic acid sensors (including retinoic acid-inducible gene-I [RIG-I]-like receptors [RLRs], cyclic guanosine monophosphate-adenosine monophosphate synthase [cGAS], 2′, 5′-oligoadenylate synthase [OAS], ds-RNA-dependent protein kinase [PKR], interferon-inducible protein 16 [IFI16], melanoma differentiation-associated gene 5 [MDA5], etc.), C-type lectin receptors (CLRs) (including Dectin 1/2, Mincle, and DC-SIGN), and inflammasome-associated ones (including caspase-4/5/11, absent in melanoma 2 [AIM2], NLRP1/3/6, and pyrin) [75] (Figure 3).

TLRs are located on the membrane, with 10 known types in humans (TLR1–TLR10) and 12 types in mice (TLR1–TLR9 and TLR11–TLR13). These receptors offer a detailed framework for how the host's immune system engages with diverse environmental stimuli, resulting in a spectrum of immune responses that can instruct and trigger the adaptive immune system. Within this expanding realm of host-environment interaction, a close link has been identified between PRRs and the signals they receive from the resident microbiota, which acts as a nexus for various environmental signals. The microbiota in mice deficient of TLRs showed significant differences in both the small and large intestines from the wild-type one [76]. TLR1's detection of the microbiota might be instrumental in regulating the colonic epithelium, thus curbing inflammation by preventing bacteria from adhering to the mucosa and by shielding the underlying immune system from exposure [77]. A malfunction in TLR1's ability in mice to identify the microbiome by the intestinal cells leads to a disturbance in the balance of the crypt cells, particularly affecting the secretory cells [77]. This includes a compromised mucus layer, the presence of misplaced Paneth cells in the colon, and an escalation in the number of rapidly proliferating cells at the crypt's base, leading to a low-grade, chronic inflammation.

The receptors of the NLR family are mainly cytosolic and are activated by pathogen-associated molecular patterns (PAMPs) (now referred to as microbe-associated molecular patterns [MAMPs]) that enter the cell or by damage-associated molecular patterns (DAMPs) produced by cellular stress. All NLRs possess the NOD, and most have a leucine-rich repeat (LRR) domain. Based on the N-terminal domain structure, NLRs are

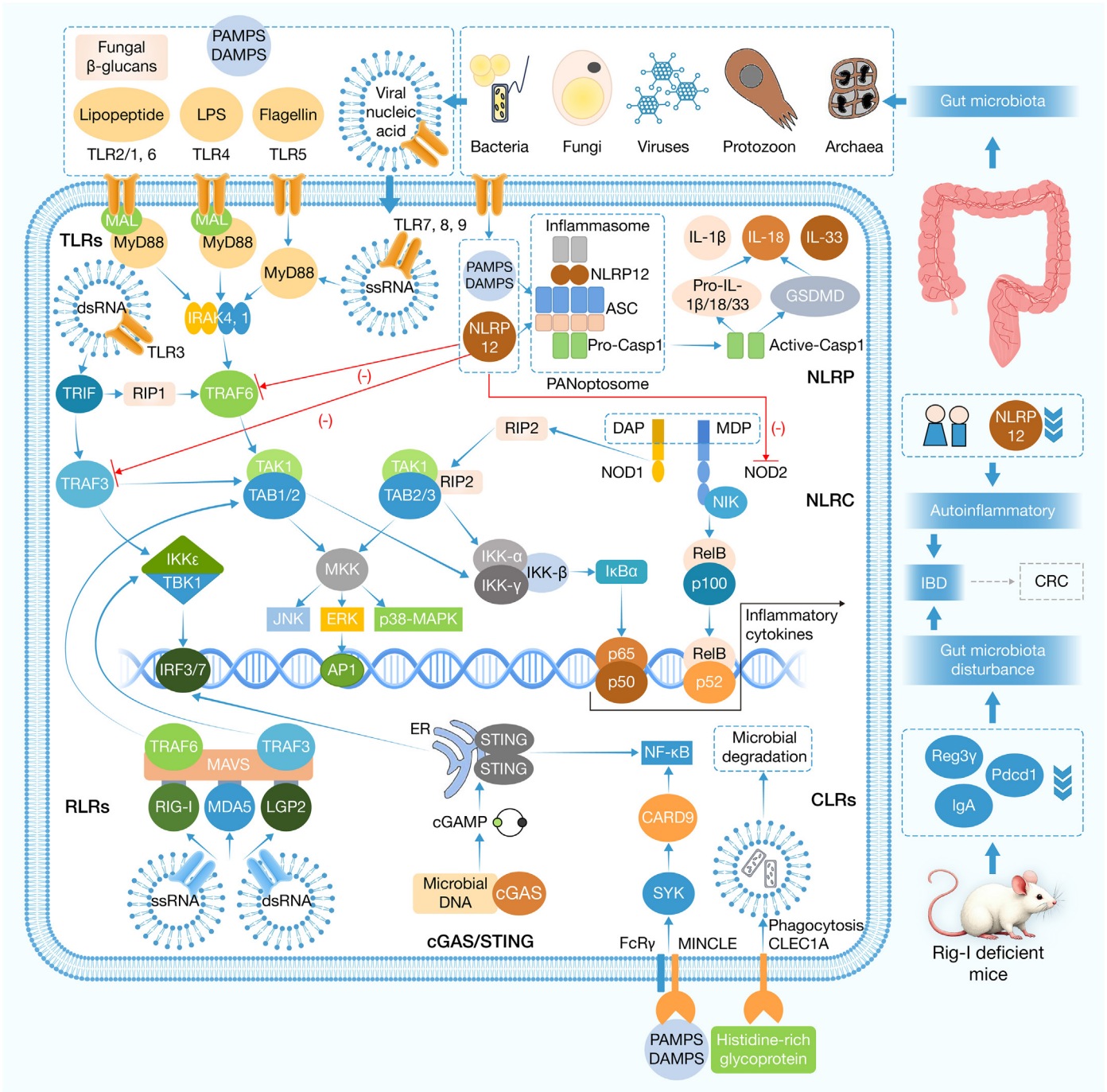

Figure 3. Interactions between gut microbiota and innate immune system

The gut microbiota, rich in bacteria, archaea, viruses, protozoa, and fungi, expresses PAMPs like LPSs and flagellin. These are detected by PRRs like TLRs, NLRs, RLRs, cGAS/STING, and CLRs, activating innate immunity. TLR activation leads to IRAK recruitment, TRAF6 poly-ubiquitination, and MAPK/NF-κB pathway activation. NLRs, with NLRC and NLRP subfamilies, respond to bacterial products, regulating inflammation and inflammasome assembly. RLRs detect RNA, linking to MAVS and TRAFs for NF-κB/IRF signaling. cGAS/STING pathway responds to dsDNA, triggering type I interferon genes. CLRs, recognizing carbohydrates, activate pathways through MINCLE and CLEC1A, influencing phagocytosis and inflammation. Abbreviations: PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; DAMPs, damage-associated molecular patterns; PRRs, pattern-recognition receptors; TLRs, toll-like receptors; NLRs, nucleotide-binding oligomerization domain (NOD)-like receptors; NLRP, NLR family pyrin domain-containing; NLRC, NLR family CARD (caspase recruitment domain) domain-containing; RLRs, retinoic acid-inducible gene-I (RIG-I)-like receptors; cGAS, cyclic guanosine monophosphate-adenosine monophosphate (GMP-AMP) synthase; STING, stimulator of interferon genes; dsDNA, double-stranded DNA; CLRs, C-type lectin receptors; IRAK, interleukin-1 receptor-associated kinase; TRAF6, tumor necrosis factor receptor (TNFR)-associated factor 6; MAVS, mitochondrial antiviral signaling protein; MAPK, mitogen-activated protein kinase; TRAFs, tumor necrosis factor receptor-associated factors; NF-κB, nuclear factor kappa B; IRF, interferon regulatory factor; MINCLE, macrophage-inducible C-type lectin; CLEC1A, C-type lectin domain family 1 member A; IBD, inflammatory bowel diseases; CRC, colorectal cancer.

classified into NLRC proteins with a CARD (caspase recruitment domain) domain and NLRP proteins with a pyrin domain (Figure 3).

These cytosolic receptors interact closely with the diverse microbial population residing in the intestine, playing a pivotal role in maintaining gut health and immune homeostasis [78]. Some NLRs facilitate this through the assembly of cytoplasmic protein complexes known as inflammasomes [79]. NLRs represent a broad category of sensors and receptors within the innate immune system. NLRs are pivotal in the recognition of pathogens, regulation of host immune responses, and control of inflammation, playing a crucial role in a variety of human diseases. They are instrumental in the initiation of caspase-1 activity, which in turn leads to the maturation and release of key inflammatory cytokines such as interleukin-1 beta (IL-1β) and interleukin-18 (IL-18). Interestingly, some members of the NLR family have been observed to suppress inflammatory responses rather than stimulate them.

NLR family pyrin domain-containing 12 (NLRP12) expression was found to be reduced in patients with active colitis [80], and this finding was corroborated in *Nlrp12*-knockout mice. The knockout mice exhibited a microbiota profile distinct from the wild-type one, displaying decreased diversity of gut microbiota and a reduced abundance of Clostridiales, Lachnospiraceae, and Bacteriodales while showing an increased abundance of Erysipelotrichaceae. Notably, a similar microbiota profile has also been observed in certain patients with IBD, further supporting the link between NLRP12 expression and microbiota composition in IBD [81]. Therefore, understanding the functional interactions between the gut microbiota and NLRs will help us to develop novel strategies for managing conditions such as colitis, IBD, and colorectal cancer (CRC) [78].

The RLR family of receptors includes RIG-I, MDA5, and laboratory of genetics and physiology 2 (LGP2), all of which contain a DExD/H box-containing RNA helicase domain that is crucial for RNA binding, and they also have a C-terminal domain (CTD) at their C-terminus. The dysbiotic gut microbiota in Rig-I-deficient mice has been demonstrated with a decreased level of immunoglobulin A (IgA) in intestines and reduced expression of IL6-STAT3-dependent Reg3γ compared to those in wild-type mice [82]. Rig-I was observed to be under-expressed in CRC tissues from both humans and mice, and mice lacking Rig-I exhibited increased vulnerability to colitis-associated CRC induced by azoxymethane (AOM)/dextran sodium sulfate (DSS). The receptors MDA5 and LGP2 are of interest to their interactions with gut microbiota because they are found to be involved in antiviral or anti-tumor signaling pathways [83].

CLRs constitute a group of transmembrane PRRs, predominantly found in myeloid cells and are adept at recognizing carbohydrates from both microbes and self-protein. Upon interaction with their ligands, CLRs can initiate intricate signaling cascades through inherent signaling sequences or by enlisting the aid of adapter proteins, thereby performing a range of cellular functions including antimicrobial responses, phagocytosis, and the production of inflammatory mediators [83].

The other cytosolic PRRs are also found to play important roles in the dialog between the host and its microbiota. The microbiota can influence the expression and function of cytosolic receptors through various mechanisms. cGAS and stimulator of interferon genes (STING) also play roles in host homeostasis through their interaction with the commensal microbiota [84]. These receptors are responsible for recognizing molecular patterns associated with invading pathogens or damaged host cells, triggering appropriate immune responses [84,85]. Gut microbiota-stimulated continuous IFN-I response was found to be dependent on the cGAS-STING pathway rather than TLR signaling or direct contact between the host and bacteria. It is the extracellular bacterial membrane vesicles (MVs) that trigger the cGAS-STING–IFN–I pathway by transferring bacterial DNA to distant host cells [85]. These MVs, containing DNA from the gut microbiota, are present in the bloodstream and have been shown to enhance the clearance of both DNA viruses, such as herpes simplex virus type 1, and RNA viruses, like vesicular stomatitis virus, in a cGAS-dependent manner (Figure 3). This research confirms the microbiota's significant function in activating the peripheral cGAS-STING pathway, thereby enhancing the host's defense against systemic viral infections.

A recent report discovered that IL-23 acts on ILC3s [86], a family of immune cells that serve as the first line of defense in mucosal tissues such as the intestines and lungs. In turn, ILC3s enhance the activity of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), a key regulatory factor that prevents the immune system from attacking the body and beneficial gut microbiota [87]. This interaction is crucial for balancing the pro-inflammatory effects of IL-23 to maintain intestinal health, but it is compromised in IBD.

The gut microbiome maintains the host's homeostasis through a multitude of mechanisms

Microbiota metabolites have been demonstrated to play roles in the maintenance of the host immune balance. A recent report uncovered a novel function of bacterial fatty acid metabolic pathways in maintaining the host's mucosal immune balance by adjusting the count of $CD4^+$ T cells that are $CD4^{+-}$ $CD8\alpha\alpha^+$ [88]. It was reported that conjugated linoleic acids (CLAs) have a reciprocal effect on a unique subset of $CD4^+$ intraepithelial lymphocytes (IELs) in the small intestine that express the CD8αα homodimer. The hepatocyte nuclear factor 4 gamma (HNF4γ) transcription factor promotes the development of $CD4^+CD8\alpha\alpha^+$ IELs by influencing the signaling pathway of IL-18 [88]. Increased levels of 5-HT in the intestinal tract can lead to a higher presence of bacteria capable of forming spores (Clostridiaceae and Turicibacteraceae) that in turn promote 5-HT production in the gut [89]. Among them, *Turicibacter sanguinis* expressing a protein related to neurotransmitter sodium symporters, bearing similarities to the mammalian serotonin transporter in terms of sequence and structure, absorbs 5-HT in a manner that can be hindered by the selective serotonin reuptake inhibitor fluoxetine [90]. The interaction between the host and *T. sanguinis* leads to changes in the expression of various intestinal gene pathways, particularly those involved in lipid and steroid metabolism, resulting in decreased levels of systemic triglycerides and reduced size of adipocytes in the inguinal region [90].

The intestinal microbial communities play a pivotal role in modulating the immune system's ability to combat cancer during treatment with immune checkpoint inhibitors. Studies in mice have pinpointed specific bacterial strains that enhance the effectiveness of anti-tumor responses to these inhibitors [91,92]. Additionally, the transfer of fecal matter from individuals who respond well to treatment has been shown to boost the success of anti-PD-1 therapies in melanoma patients [93,94]. The gut microbiome can suppress the expression of PD-L2 and its associated molecule, repulsive guidance molecule b (RGMb), thereby fostering an anti-tumor immune response, highlighting the reduction of the PD-L2-RGMb pathway as a distinct mechanism used by the gut microbiota to enhance the efficacy of PD-1 checkpoint inhibitors [95]. The transfer of gut microbiota-derived outer membrane vesicles (OMVs) into the intestinal tract can mitigate the effects of colitis and boost the efficacy of anti-PD-1 treatments for CRC in animal experiments by modulating the intestinal balance [96].

The crosstalk between the microbiota and the intestinal physicochemical barrier, which is crucial for gut innate immunity, has been widely studied. The microbiota helps maintain the integrity of tight junctions in epithelial cells, enhancing host barrier function [97]. OMVs released from *Akkermansia muciniphila* are able to enter intestinal epithelial cells to stimulate the expressions of tight junctions and mucus [96]. The microbiota produces antimicrobial substances such as bacteriocins and lysozymes, assisting the host in resisting invasion by foreign pathogens [98–100]. The microbiota regulates the secretion of the mucus layer, enhancing its antibacterial activity and helping the host to resist the invasion of foreign pathogens. The symbiotic *Escherichia coli* strain 8178 uses a strategic ruse akin to the Trojan horse to curb the proliferation of *Salmonella enterica* serovar Typhimurium in the inflamed intestinal tract [98]. OMVs from *A. muciniphila* were also found to trigger a mucosal IgA response by penetrating Peyer's patches, thereby initiating the activation of B cells and dendritic cells [96]. An antibacterial lectin RegIIIγ is secreted by Paneth cell stimulated by short-chain fatty acids from microbiota and plays a key role in preserving a separation zone of approximately 50 μm between the microbiota and the epithelial lining of the small intestine. In the absence of RegIIIγ in mice, the loss of this spatial separation leads to increased colonization of the intestinal epithelium by bacteria and a heightened activation of the intestinal adaptive immune system in response to the microbiota [101].

Chronic Inflammation in Disease Development and its Mechanisms

Chronic low-level inflammation is a defining feature of metabolic conditions including IBD, T2D, obesity, non-alcoholic fatty liver disease (NAFLD), etc. (Figure 1). Gut microbiota also plays a role in human adaptation to high altitudes [102]. Recent studies suggest that these illnesses are often marked by shifts in the gut microbiota's composition and its byproducts, which can pass through an impaired intestinal barrier to impact distant metabolic tissues like the liver and fat, positioning to a great extent the gut microbiota a key driver of metabolic inflammation and its associated dysregulation [21]. Due to the correlation between gut dysbiosis and nearly all diseases from the head to toe, only a few diseases are listed in the following stanzas as representatives for discussion.

Aging

The concept of inflammaging emerges for describing a persistent, sterile, and low-grade inflammatory state as individuals age. It is a significant and fundamental mechanism in the process of aging and the development of diseases related to aging [103]. As mentioned earlier, in the context of metabolic diseases, a specific type of chronic inflammation known as metaflammation arises from nutrient surplus or overnutrition, and it operates through mechanisms like those of inflammaging. The gut microbiota plays a crucial role in both metaflammation and inflammaging due to its capacity to produce inflammatory substances, regulate circadian rhythms, and interact with other bodily systems. Aging is a complex process involving the interplay of multiple factors, including human organs, microbiota, nutrients, medicine taken, environmental parameters, etc., and the imbalance of these interactions leading to chronic inflammation plays a significant role in promoting the occurrence and development of aging and age-related chronic diseases. Therefore, assessing, preventing, and controlling chronic low-grade inflammation are important means of anti-aging. The cGAS-STING signaling pathway, which is responsible for the immune system's detection of DNA, has been demonstrated to play an essential role in the development of persistent inflammation and the deterioration of physiological functions with age [104]. This pathway contributes to inflammation associated with aging in both peripheral tissues and the brain. Cytoplasmic DNA from dysfunctional mitochondria activates cGAS in aged microglia, outlining a pathway for the involvement of cGAS-STING signaling in the aging brain, indicating that targeting the cGAS-STING signaling could be a promising approach to mitigate neurodegenerative processes in later life [104]. A recent report indicates that interleukin-11 (IL-11), an inflammatory mediator in the interleukin-6 (IL-6) family, is involved in the health and longevity of mammals [105]. The potential of anti-IL-11 therapies, which are in the preliminary stages of clinical testing for pulmonary fibrosis, warrants further exploration into their capacity to combat age-associated pathologies, highlighting a promising avenue in the field of anti-aging medicine.

Inflammatory bowel disease

IBD encompasses Crohn's disease and ulcerative colitis, serving as quintessential examples where dysbiosis-driven inflammation plays a pivotal role in disease onset and exacerbation [81]. Studies have consistently demonstrated a notable surge in the population of facultative anaerobes at the expense of their obligate counterparts, accompanied by disruptions in the transcription processes of microbes, exemplified by the changes observed in clostridia, metabolite pools, and levels of antibodies in host serum [106].

Obesity and type 2 diabetes

Metabolic disorders such as obesity and T2D exhibit strong associations with dysbiosis-induced chronic inflammation [24,49]. Obesity is often linked to a state of chronic, low-level inflammation within tissues that play a role in metabolism. Research

indicates that the insulin resistance associated with obesity is caused by inflammation's detrimental impact on crucial proteins within the insulin signaling cascade [107]. Several mechanisms have been pinpointed as initiators of the metabolic inflammation tied to obesity, including endoplasmic reticulum (ER) stress, activation of toll-like receptor 4 (TLR4), and alterations in the gut microbiota. These mechanisms are seen as promising therapeutic targets for managing obesity and its related health issues. The evidence positions TLR4 as a central component in the chain of events linking dietary fat intake to metabolic inflammation and insulin resistance [107]. Disruptions in the gut microbiota can compromise the intestinal barrier's integrity, increasing the permeability that allows LPSs and fatty acids to seep through. These substances can then engage TLR4, initiating a systemic inflammatory response. Additionally, fatty acids have the potential to induce ER stress, which can be exacerbated by interactions with an activated TLR4. Consequently, the existing data suggest an interconnection among the primary instigators of metabolic inflammation, with TLR4 serving as a common thread weaving through these various mechanisms [107].

Dysbiotic alterations in the gut microbiota have been correlated with low-grade systemic inflammation in obese individuals and those with insulin resistance [49], highlighting the role of chronic inflammation in deciphering the intricate links between dysbiosis, metabolic disturbances, and inflammatory pathways. Strategies that target the modulation of gut bacteria to enhance treatment outcomes for T2D and associated disorders are promising [108]. Comprehensive analysis of 8117 whole-genome sequences of participants across 10 different cohorts from the United States, Europe, Israel, and China, spanning a range of glycemic states, including those with T2D, prediabetes, and normal blood sugar levels, revealed that 19 taxonomically varied species showed a significant correlation with T2D. Notably, an increase in *Clostridium bolteae* and a decrease in *Butyrivibrio crossotus* were observed in association with T2D [9]. This report further uncovered intra-species phylogenetic variation among 27 species that may account for variations in T2D risk among individuals, exemplified by *Eubacterium rectale*. Using mouse models that mimic gestational diabetes mellitus (GDM) induced by transplantation of fecal microbiota from women with GDM, a report found that a decrease of SCFA-producing microbes, especially those producing propionate and butyrate [109], resulted in inflammation triggered by LPSs through the TLR4-nuclear factor kappa B (NF-κB) pathway and activation of adipose tissue macrophages toward an M1 phenotype, which is known to contribute to insulin resistance. These findings offer a novel perspective on the development of GDM and may pave the way for new therapeutic approaches.

Diabesity, a term that encapsulates both T2D and obesity, is marked by ongoing, mild inflammation. The Wnt signaling pathway is a fundamental biological mechanism that is instrumental in maintaining cellular equilibrium and managing energy balance across various bodily systems, from the hypothalamus to metabolic tissues [110]. Disruptions in the activity of components within the canonical and non-canonical Wnt pathways can disrupt metabolic processes, resulting in the enlargement of adipose tissue [111]. This pivotal change can set off metabolic stress, which in turn triggers a state of low-grade, chronic inflammation known as metaflammation [112,113], a precursor to obesity. The metaflammation-associated obesity can lead to the abnormal growth of adipocytes, a process that involves the non-canonical Wnt signaling's suppression of the canonical Wnt pathway, thereby exacerbating the process of adipogenesis. Additionally, the activation of TLR4 signaling under metabolic stress can prompt immune cells to emit pro-inflammatory cytokines. This attracts macrophages into adipose tissue, leading to their polarization into two subtypes: M1 (classically activated) and M2 (alternatively activated). These processes culminate in chronic, low-grade inflammation, which disrupts insulin signaling in metabolic tissues, potentially leading to the development of T2D [114].

Nonalcoholic fatty liver disease

Gut dysbiosis triggers local inflammatory responses and ER stress, leading to the production of inflammatory cytokines that worsen intestinal permeability. The leakage from the gut, characterized by the passage of LPSs, bacterial acetate, and SCFAs to the liver through the portal vein, fosters the progression of hepatic *de novo* lipogenesis and inflammation, thereby emphasizing the pivotal role of the gut–liver axis in the pathogenesis of non-alcoholic steatohepatitis and NAFLD [115]. Gut microbiota plays a crucial role in gut–liver repair [116].

Cancer

Microbiota dysbiosis is related to the development of cancers [117]. Several pathobionts have been reported to be associated with development of CRC [33,118,119], including *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis*, polyketide synthase-positive (pks$^+$) *E. coli*, *Peptostreptococcus anaerobius*, *P. micra*, *Clostridium septicum*, *Porphyromonas gingivalis*, *Streptococcus bovis*, and some fungi [120], Archaea [121], and viral communities [122]. These pathobionts can induce or promote carcinogenesis by genomic integration, genotoxicity, inflammation, immunity, and/or metabolism [117]. For example, *F. nucleatum* facilitates the development of CRC by triggering the activation of TLR4, which initiates myeloid differentiation primary response gene 88 (MYD88) signaling, thereby enhancing NF-κB activity and the expression of miR21, ultimately leading to the suppression of RAS GTPase RASA1 [123]. This bacterium can also fuel the carcinogenic process in CRC by amplifying cellular glucose metabolism, achieved through the elevation of long non-coding RNA (lncRNA) ENO1-IT1 mediated by SP1, which orchestrates KAT7-driven histone modifications, thereby reshaping the cellular biology of CRC [124]. Biofilm formed by colibactin-producing *E. coli* and enterotoxigenic *Bacteroides fragilis* (ETBF) on the colon neoplasia might induce CRC, which was confirmed in a tumor-prone mouse model, where coinfection with the two bacteria increased DNA damage in colonic epithelial cells for tumor development [125]. *E. coli*-generated colibactin results in the incorporation of a rare electrophilic cyclopropane during DNA alkylation, a process occurring in

the colons of mice infected with colibactin-producing *E. coli*, and this is believed to be a conversion from a primordial, unstable colibactin-DNA adduct [126]. MiR-149–3p, carried by exosomes from cells treated with ETBF, promotes the differentiation of Th17 cells. The ETBF-driven carcinogenic process in CRC relies on the reduction of miR-149–3p, which in turn enhances PHF5A-dependent alternative RNA splicing of KAT2A in CRC cells [127]. *P. anaerobius* engages with TLR2 and TLR4 on the surface of colon cells, leading to an elevation in reactive oxidative species, thereby enhancing cholesterol production and cell growth [128]. *Clostridium symbiosum* can stimulate cellular cholesterol synthesis to foster tumor growth [129]. *P. gingivalis* triggers an increase in the expression of CHI3L1 within invariant natural killer T (iNKT) cells [130]. *Desulfovibrio vulgaris* stimulates the LRRC19/TRAF6/TAK1 signaling pathway through its flagellin [131]. *P. micra* elevates the expression of miR-218–5p, which leads to the suppression of PTPRR and subsequently triggers the Ras/extracellular regulated protein kinase (ERK)/c-Fos signaling pathway, thereby advancing CRC [33]. The surface protein TmpC of *P. micra* interacts with the receptor CKAP4, enhancing the bacterium's ability to adhere to and invade host cells [132]. These in-depth studies of the mechanisms involving gut pathobionts and CRC have opened new avenues for the diagnosis, treatment, and prevention of the disease.

The interactions between diet and the microbiome influence the colonization of the intestines by opportunistic and tumorigenic bacteria. Diet may proliferate specific gut bacteria to either initiate colorectal epithelial carcinogenesis or foster a tumor-supportive immune environment, and the impacts of various dietary modifications on the microbiome and on cancer outcomes should be elucidated [133]. The interaction between TLR5 and the resident microbiota influences the systemic inflammatory response that promotes tumor growth and the spread of malignancies to other body regions [134].

Neurological conditions

The gut microbiome has a regulatory effect on the proper maturation of the somatic peripheral nervous system and its functional interaction with skeletal muscles, thereby the concept of a new "gut microbiota–peripheral nervous system axis" was proposed [135]. Emerging evidence also points to neurodegenerative diseases, like Alzheimer's and Parkinson's, where dysbiosis-induced inflammation may influence disease progression [136,137]. Dysregulation of the gut–brain axis due to alterations in gut microbiota composition and subsequent inflammatory responses has been proposed as a potential contributing factor in these neurological conditions. The gut microbiome in individuals suffering from depression with inflammatory characteristics is characterized by elevated levels of *Bacteroides* and reduced *Clostridium*, alongside an upregulation of SCFA-producing species, particularly those with irregular butanoate metabolism, indicating that the gut's inflammatory processes may play a role in the neuroinflammation associated with depression [138].

Elevated blood pressure

It is a major health concern for communities worldwide. New insights indicate that a shift in the composition of the gut microbiota may contribute to the development of high blood pressure (BP). One potential pathway involves the ongoing transfer of gut microbes' components, particularly LPSs, into the bloodstream, which can result in a state of low-grade systemic inflammation known as metabolic endotoxemia [139]. Clinical studies have found a correlation between blood plasma LPS levels and high BP. A comprehensive review proposes that the direct impact of LPS on blood vessel linings can lead to hypertension [139]. The LPSs' role in activating TLR4 on endothelial cells sets off a series of interconnected signaling pathways: first, the NADPH oxidase/reactive oxygen species (ROS)/endothelial nitric oxide synthase (eNOS) pathway, which can cause endothelial dysfunction; and second, the mitogen-activated protein kinase (MAPK) and NF-κB pathways, which can lead to vascular inflammation. Randomized controlled trials and systematic reviews have provided some evidence supporting the anti-inflammatory effects of probiotics, with a statistically significant reduction in BP in clinical populations, suggesting probiotics as a potential strategy for hypertension management [139].

Atherosclerosis

Gut microbiota affects the progression of atherosclerosis triggering chronic inflammation, affecting bile acid metabolism, and altering the effects of metabolic products [57,140]. The persistent low-grade inflammation triggered by dysbiosis leads to the aggregation and deposition of various cells on the vascular wall, forming a vicious cycle that promotes the formation of atherosclerosis [35,141]. When the microbiota is disrupted, the production of bile acids decreases, affecting the normal metabolism of cholesterol, and leading to the accumulation of cholesterol in the body, thereby exacerbating atherosclerosis. Metabolic products such as SCFAs produced by the gut microbiota are crucial for cardiovascular health. The dysbiotic microbiota can lead to abnormal increases in metabolic products like TMAO and indoxyl sulfate, which can promote the progression of atherosclerosis [142,143].

Endometriosis

It is recognized as a complex and chronic inflammatory condition that can manifest in various body areas, distinguished by the estrogen-fueled cyclical bleeding, growth, and scarring of misplaced endometrial tissue beyond the uterus. The limited understanding of its root causes and intricate pathophysiology makes early detection and effective, low side-effect treatment challenging. A strong link between the gut microbiota, inflammation, estrogen processing, and immune function is demonstrated recently in the onset and progression of endometriosis. Understanding of the multifaceted mechanisms connecting endometriosis with the gut microbiota will offer novel strategies for prevention, early detection, and management of the condition [144].

Ocular diseases

Gut microbiota-derived SCFAs can influence ocular inflammation and immune responses through the G-protein-coupled receptor 43 (GPR43) [145]. A report showed that sodium butyrate notably reduced the inflammatory effects induced by various TLR agonists, such as poly(I:C), flagellin, and CpG-ODN (activators of TLR3, TLR5, and TLR9, respectively), in wild-type mice, an effect absent in *GPR43* knockout mice. The mitigating impact of butyrate on TLR-induced keratitis was mediated by GPR43 in non-hematopoietic tissue cells.

CHALLENGES AND FUTURE DIRECTIONS IN INFLAMMATOMICS

Challenges in Studying Inflammatomics

Despite its immense potential, the field of inflammatomics faces several challenges that hinder its widespread application in clinical settings. Technological limitations, particularly in high-throughput sequencing and multi-omics data integration, pose significant hurdles. The complexity of the human microbiome and the vastness of omics data generated from studies exploring dysbiosis-induced chronic inflammation require sophisticated analytical tools and computational resources. Integrating diverse data sets, including metagenomics, metatranscriptomics, metabolomics, and metaproteomics [146], presents a formidable challenge due to the intricate interactions between host and microbial factors both within the host and surrounding the host.

Additionally, each technology has varying sensitivities in acquiring relevant data. Each analytical method captures incomplete partial data from different perspectives. The integration of partial data from multiple analytical techniques can amplify the local shortcomings of the data, leading to one-sidedness in the analysis results by introducing data bias by different methods. This is one of the dilemmas of big data in biology.

Significant challenges in sample processing, omics data acquisition, and data analysis have limited sensitivity and data completeness, primarily due to the complexity and high heterogeneity of microbial community samples. For extracting DNAs from fecal samples, the bacterial lysis efficiency greatly influences the sequencing data followed because the bacterial diversities in the sample vary tremendously, and the bioinformatic arithmetic also impacts the accuracy of the data processing and analysis [147]. For metaproteomic analyses, optimization of preprocessing methods for different types of samples and the adoption of various microbial isolation, enrichment, extraction, and lysis strategies are often necessary. The analysis of data-independent acquisition (DIA) data is challenged by the complexity of metaproteomic samples, which hinders deeper coverage of the metaproteome [148]. Despite substantial advancements, hurdles persist in the precision of predictive models and the comprehensiveness of reference databases, which constrain the utility of omics methods in less-studied ecological systems. The amalgamation of computational resources with multi-omic datasets is poised to enhance personalized strategies in precision health care, enabling strategic interventions that adjust the microbiome to enhance health outcomes [149].

Moreover, standardization and reproducibility across inflammatomics studies remain a concern. Variability in study designs, sample collection methods, and data analysis pipelines makes it challenging to compare findings across different research endeavors. Establishing robust protocols and benchmarks for data acquisition, processing, and interpretation is crucial for ensuring consistency and reliability in inflammatomics research. Figure 4 illustrates a generic workflow for inflammatomics research, comprising the following sequential steps. Data acquisition involves step 1: microbiota and blood sampling, symbolizing the methods of sample collection, and step 2: multi-omics data generation, showing various omics techniques and the determination of gut barrier biomarkers. Data integration and analysis include step 3: data integration, merging, and processing multi-omics data, and step 4: computational analysis, representing the analytical methods and tools used. Inflammation profiling is achieved through step 5: inflammatory biomarker identification and step 6: inflammatory pathway mapping, illustrating the discovery and characterization of biomarkers and the mapping of pathways linked to dysbiosis-induced inflammation. Disease association is depicted in step 7: disease correlation, with arrows connecting inflammation profiles to disease representations. The final stages, precision medicine and interventions, include step 8: precision medicine applications representing personalized treatments, and step 9: public health strategies, symbolizing community health implications based on inflammatomics research.

Another significant challenge lies in deciphering causal relationships between dysbiosis, inflammation, and disease outcomes. While associations have been established between altered microbial communities and inflammatory states, delineating the precise mechanisms driving these relationships requires further investigation. Untangling whether dysbiosis is a cause or consequence of chronic inflammation in specific diseases remains a complex task.

Future Directions and Advancements

Addressing the current challenges faced by inflammatomics demands a multidisciplinary approach involving technological innovations, standardization efforts, collaborative initiatives, longitudinal studies, and consensus definitions.

Culturomics technology is crucial for obtaining microbial strains and conducting in-depth research on the interactions between strains and hosts. High-throughput targeted microbial isolation and culture technology are urgently in need of development [150]. Advancements in high-resolution omics technologies, such as single-cell sequencing and spatial transcriptomics, hold promise in unraveling the complexities of host-microbiota interactions at a finer scale. These technologies can provide deeper insights into the heterogeneity of microbial communities and host responses, allowing for a more comprehensive understanding of dysbiosis-induced chronic inflammation.

Furthermore, the development of advanced computational models, machine learning (ML) algorithms, and artificial intelligence (AI) applications tailored for analyzing multiomics data will be instrumental. These tools can aid in integrating large-scale omics datasets, identifying key microbial signatures, and predicting inflammatory responses, thus facilitating the translation of complex data into clinically actionable insights.

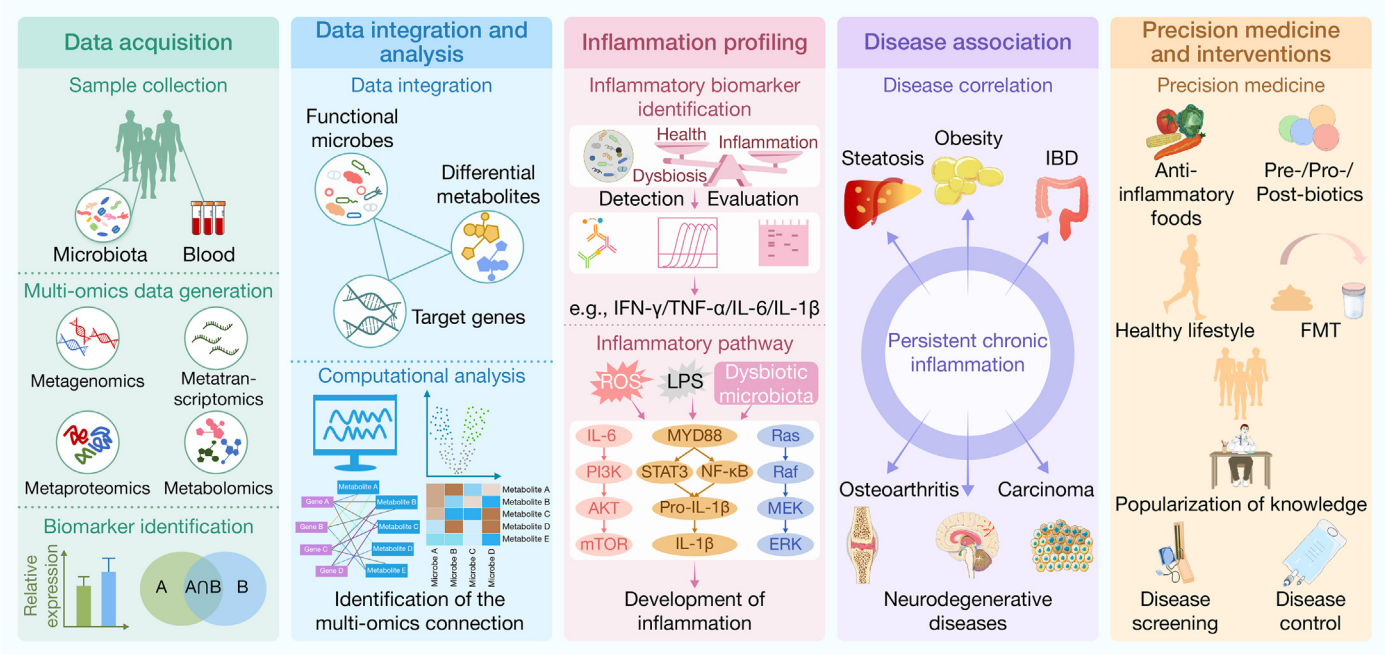

Figure 4. Research outline on inflammatomics
The general workflow in inflammatomics research is illustrated, encompassing data acquisition, integration and analysis, inflammation profiling, disease association, and the application of precision medicine/interventions. Abbreviations: IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; ROS, reactive oxygen species; LPS, lipopolysaccharide; PI3K, phosphatidylinositol-3-kinase; AKT/PKB, protein kinase B; mTOR, mammalian target of rapamycin; MYD88, myeloid differentiation primary response gene 88; STAT3, signal transducer and activator of transcription 3; MEK, mitogen-activated extracellular signal-regulated kinase, ERK, extracellular regulated protein kinase; IBD, inflammatory bowel disease; FMT, fecal microbiota transplantation.

Standardization efforts and the establishment of consortia or collaborative initiatives are essential to address the reproducibility and comparability issues in inflammatomics research. Collaborative projects focusing on harmonizing methodologies, sharing protocols, and creating centralized repositories for multiomics data can enhance data quality, reproducibility, and facilitate meta-analyses across diverse cohorts.

Moreover, longitudinal studies and intervention trials exploring the dynamics of dysbiosis-induced inflammation over time and in response to specific interventions are imperative. Investigating the effects of microbiota-targeted therapies, dietary modifications, or microbial interventions on inflammatory profiles can provide crucial insights into causal relationships and therapeutic strategies.

Additionally, incorporating multiomics data into clinical practice requires the development of consensus definitions, validated biomarkers, and diagnostic tools. Translation of inflammatomics findings into clinically relevant biomarkers that can guide personalized interventions and monitor treatment responses is pivotal for the integration of inflammatomics into routine healthcare settings.

The study of inflammatomics will lay the theoretical and practical foundation for health maintenance across the entire lifespan (Figure 5). By delving into the mechanisms by which the microbiome–host balance is affected by internal and external factors and the underlying logic of chronic low-grade inflammation it induces, this research will point the way toward the development of new strategies for health maintenance. Recently, a pivotal gut bacterium, *Bacteroides xylanisolvens* C3, was found to degrade the food-grade lambda-carrageenans (L-CGNs), and the degraded L-CGNs markedly elevated nitric oxide and cyclooxygenase-2 (COX-2) levels and induced the expression of pro-inflammatory genes like IL-1β, TNF-α, and IL-6 in macrophages [151]. These findings imply that the microbial breakdown of L-CGN in the digestive tract may play a role in inflammatory processes, emphasizing the necessity for a deeper comprehension of the interplay between gut microbes and food-grade L-CGN, especially about colon health and inflammation-related conditions such as IBD. However, another report showed that *B. xylanisolvens* XB1A could degrade xylan to produce SCFAs and folate [152], which are beneficial to health. These studies further illustrate the complexity of understanding the interaction mechanism between gut microbiota and food. It is essential that we comprehend the role of gut microbiota in the intestinal microecosystem from the perspective of individual strains, laying the foundation for precise interventions. The potential next-generation probiotics have been reported to play beneficial roles in alleviating some diseases. *Parabacteroides distasonis* has been demonstrated to achieve neuroprotection in cases of acute ischemic stroke accompanied by hyperuricemia through the modulation of the gut microbiota–gut–brain axis [153]. This bacterium also plays roles in therapeutic effects on enterohepatic disease [154] and interacts with traditional Chinese medicine [155]. The

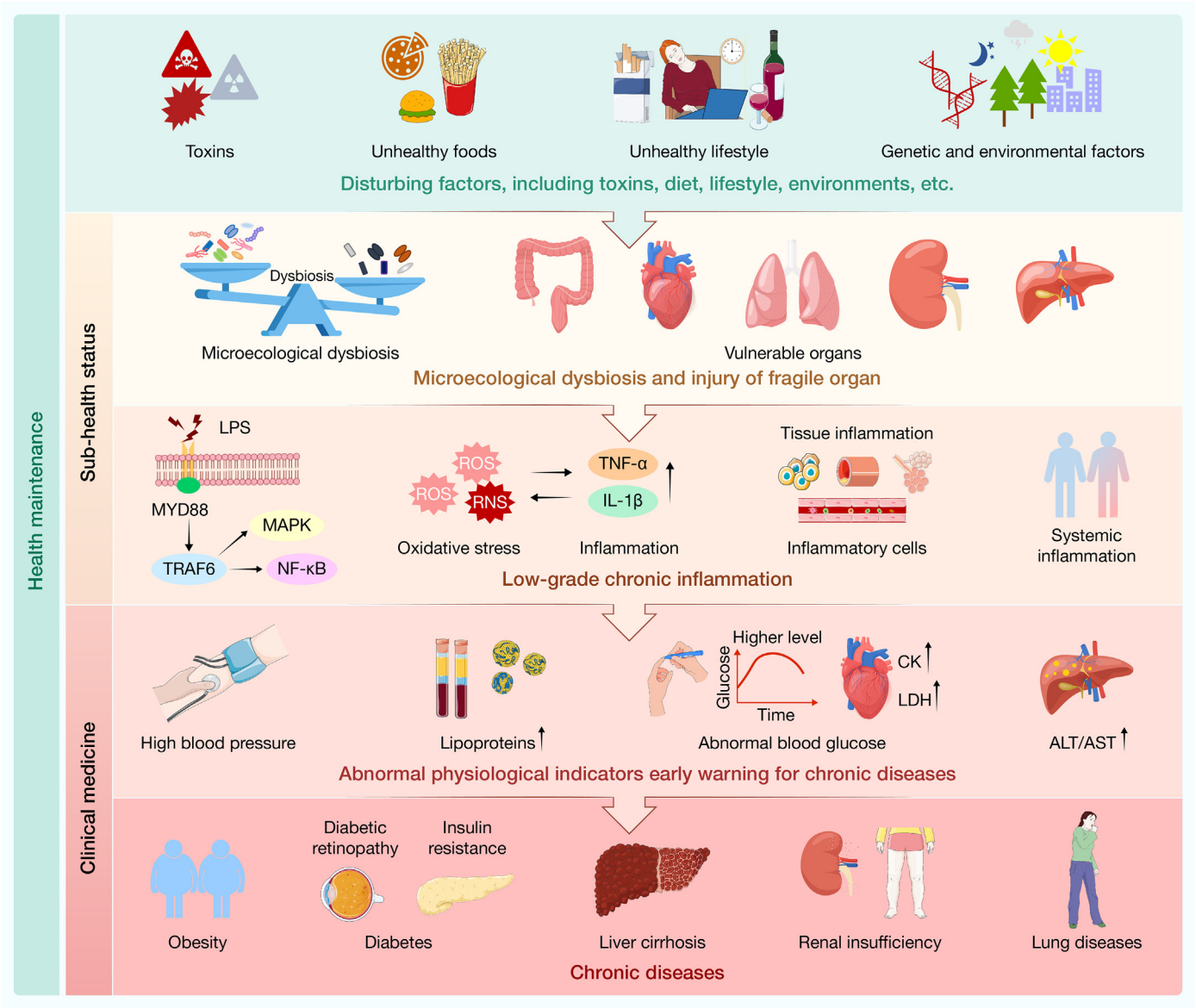

Figure 5. Health maintenance for the whole life cycle, illustrating the progression from health to chronic diseases
On the left-hand side, "health maintenance" is shown as the initial state. Disturbing factors such as toxins, diet, lifestyle, and environment can disrupt this state, leading to sub-health. Sub-health is potentially caused by microecological dysbiosis and injury of fragile organs. This, in turn, triggers low-grade chronic inflammation. As the condition deteriorates, abnormal physiological indicators, which serve as early warnings for chronic diseases, emerge. Eventually, these indicators may progress to full-blown chronic diseases. Early recognition of sub-health status and timely intervention of the health maintenance countermeasures will help prevent and control of chronic diseases, and if, unfortunately, the chronic diseases develop, the early diagnosis and clinical interventions are also effective for preventing their deterioration. Abbreviations: LPS, lipopolysaccharide; MYD88, myeloid differentiation primary response gene 88; TRAF6, tumor necrosis factor receptor-associated factor 6; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; RNS, reactive nitrogen species; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

presence of *P. merdae* in the gut guards against cardiovascular injury by promoting the breakdown of BCAAs [57]. The westernized lifestyles can make some ancient core members of the human gut virome thrive, associated with diabetes, IBD, etc. [156]. The re-emerging bacteriophage therapy has shown promise for treating IBD [157]. Mushroom polysaccharides, a potential prebiotic, are mainly broken down into fatty acids by microbiota, enriching probiotic bacteria, such as *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus*, while repressing the proliferation of detrimental bacteria like *Escherichia* and *Shigella*, highlighting its considerable promise for disease prevention through improved intestinal health [158,159].

The application of AI and ML in analyzing multi-omics data from the gut microbiome will help us to cope with the challenges of integrating these large datasets, including data heterogeneity, incompleteness, scarcity, the lack of standardization, computational complexity, high dimensionality, scalability issues, limited tool accessibility, biological and clinical interpretability, causal relationship identification, and ethical and privacy concerns

[160]. Addressing these challenges requires multidisciplinary collaboration, standardized protocols, data imputation, validation, quality control, the development of advanced algorithms, and increased computational resources [160]. AI and ML offer promising solutions and ensure reliable and meaningful insights from complex, large-scale datasets, enabling the discovery of microbial biomarkers for disease classification, predicting treatment responses, and personalizing microbiome-modulating therapies [160,161].

CONCLUDING REMARKS AND PERSPECTIVES

Inflammatomics for uncovering mechanisms of inflammatome is a pioneering field that stands and develops as a powerful tool elucidating the intricate connections between dysbiosis-induced chronic inflammation and disease pathogenesis across various conditions. It integrates multi-omics data and microbiota interactions, providing insights into managing and preventing chronic diseases. This approach not only clarifies disease mechanisms, identifies biomarkers for diagnosis, and monitors treatment efficacy but also guides microbiota-based therapies and personalized treatments. Inflammatomics also influences public health by enabling preventive strategies based on inflammatory profiles. Continued research and clinical application are crucial for realizing its full potential in health care.

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DECLARATION OF COMPETING INTERESTS

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

AUTHOR CONTRIBUTIONS

Huan Zhang: investigation, visualization, writing – original draft. **Bing Jun Yang Lee:** investigation, writing – review & editing. **Tong Wang:** investigation, visualization. **Xuesong Xiang:** investigation, writing – review & editing. **Yafang Tan:** investigation. **Yanping Han:** investigation. **Yujing Bi:** supervision, investigation. **Fachao Zhi:** investigation. **Xin Wang:** investigation. **Fang He:** investigation. **Seppo J. Salminen:** conceptualization, writing – review & editing. **Baoli Zhu:** conceptualization, writing – review & editing. **Ruifu Yang:** conceptualization, supervision, funding acquisition, writing – review & editing.

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