

PERSPECTIVE ARTICLE

NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome at the crossroads of dysbiosis and disease: A target for microbiome-modulated inflammation

Shishir Singh¹, Rajeev Nema², Monisha Banerjee³, and Atar Singh Kushwah^{4*}¹Department of Medicine, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York City, New York, United States of America²Department of Biosciences, School of Physical and Biological Sciences, Faculty of Science, Technology and Architecture, Manipal University Jaipur, Jaipur, Rajasthan, India³Molecular and Human Genetics Laboratory, Department of Zoology, Faculty of Sciences, University of Lucknow, Lucknow, Uttar Pradesh, India⁴Translational Oncology and Women's Health, Department of Biosciences, School of Physical and Biological Sciences, Faculty of Science, Technology and Architecture, Manipal University Jaipur, Jaipur, Rajasthan, India***Corresponding author:**Atar Singh Kushwah
(atar.kushwah@jaipur.manipal.edu)**Citation:** Singh S, Nema R, Banerjee M, Kushwah AS. NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome at the crossroads of dysbiosis and disease: A target for microbiome-modulated inflammation. *Gene Protein Dis.* 2026;5(3):025180034. doi: 10.36922/GPD025180034**Received:** May 1, 2025**Revised:** December 24, 2025**Accepted:** January 4, 2026**Published online:** January 22, 2026**Copyright:** © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.**Abstract**

The NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome is a critical regulator of inflammation and innate immunity, linking microbial and environmental signals to inflammatory responses. Dysbiosis, an imbalance in the composition of the microbiota, is increasingly recognized as a key trigger for aberrant NLRP3 activation. Under healthy conditions, NLRP3 protects against pathogens and maintains homeostasis; however, chronic activation driven by dysbiosis promotes low-grade inflammation and contributes to various diseases. In the gut, dysbiosis-induced NLRP3 activation is implicated in inflammatory bowel disease, colorectal cancer, obesity, and metabolic disorders. Beyond the gut, dysbiosis in the vaginal microbiome, oral cavity, and skin can activate the NLRP3 inflammasome, driving conditions, such as bacterial vaginosis, periodontitis, and chronic inflammatory skin diseases. Emerging evidence also links dysbiosis-associated NLRP3 activation to neurodegenerative disorders and autoimmune diseases, where systemic inflammation and microbiome disturbances accelerate disease progression. Understanding the mechanisms by which dysbiosis activates the NLRP3 inflammasome is critical for developing targeted therapeutic strategies. Interventions aimed at restoring microbial balance—such as dietary modification, probiotics, and inflammasome inhibitors—may offer promising approaches to mitigate NLRP3-driven inflammation and improve human health outcomes. This perspective highlights the complex interplay between dysbiosis and NLRP3 activation, with a focus on its role in health and disease and on emerging therapeutic strategies to restore homeostasis.

Keywords: NLRP3 inflammasome; Dysbiosis; Chronic inflammation; Microbiota; Immune homeostasis; Therapeutic interventions

1. Introduction

The human microbiome plays a pivotal role in maintaining health and regulating immune homeostasis. Dysbiosis, an imbalance in the composition and function of the microbiota, has emerged as a key driver of various chronic inflammatory and metabolic diseases.¹ One critical molecular pathway implicated in dysbiosis-induced pathogenesis is the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome. The NLRP3 inflammasome functions as a context-dependent immune sensor that integrates signals from microbial composition, metabolic stress, and environmental cues to calibrate inflammatory tone. While transient activation supports host defense and tissue repair, sustained NLRP3 signaling driven by dysbiosis promotes chronic inflammation and disease progression.¹⁻³

Emerging evidence highlights a bidirectional relationship between dysbiosis and NLRP3 activation. Dysbiosis can directly activate the NLRP3 inflammasome through microbial toxins, metabolites, and reactive oxygen species (ROS), while sustained NLRP3 activation can, in turn, reshape microbial composition, creating a self-perpetuating cycle of chronic inflammation.³

Here, we discuss the complex interplay between NLRP3 activation and dysbiosis, with a focus on its impact on human health. We highlight the underlying molecular mechanisms by which dysbiosis triggers NLRP3 inflammasome activation, the role of microbiome alterations in perpetuating chronic inflammation, and the clinical implications for diseases associated with this axis. We also explore potential therapeutic strategies, including microbiome modulation and inflammasome inhibitors, aimed at restoring microbiota balance and mitigating NLRP3-driven pathologies.

2. NLRP3–microbiome axis: A cycle of inflammation and dysbiosis

The NLRP3 inflammasome plays a crucial role in maintaining gut immune balance by detecting microbial and cellular stress signals. Importantly, the relationship between NLRP3 and the gut microbiota is bidirectional. While microbial dysbiosis can stimulate NLRP3 activation, a persistently active inflammasome, in turn, can reshape microbial communities, establishing a self-reinforcing cycle that sustains chronic inflammation.^{4,5} Such reciprocal interactions have been implicated in disorders, including inflammatory bowel disease, obesity, and neurodegenerative conditions.^{6,7} For example, expansion of pro-inflammatory bacterial groups, such as *Proteobacteria* is associated with heightened NLRP3 activation, whereas beneficial microbial metabolites,

particularly short-chain fatty acids (SCFAs), exert inhibitory effects on inflammasome signaling and promote immune homeostasis.⁸ This bidirectional feedback loop between microbiome dysbiosis and NLRP3 inflammasome activation, and its downstream consequences for epithelial barrier integrity and chronic inflammation, is schematically illustrated in [Figure 1](#).

Targeting NLRP3 directly or restoring microbial balance through dietary interventions and probiotics has shown therapeutic promise in pre-clinical models of colitis and metabolic disease.^{9,10} Notably, this gut–immune axis extends beyond the intestine to the central nervous system, where altered microbiota composition and NLRP3-driven inflammation have been linked to mood disorders and neurodegeneration.^{11,12} Future research should further delineate these mechanisms and identify context-specific opportunities for therapeutic intervention.

3. NLRP3 inflammasome activation: Balancing immune defense and tolerance

The NLRP3 inflammasome is a central component of the innate immune system that senses microbial and cellular stress signals. Pathogens, such as *Staphylococcus aureus* and *Porphyromonas gingivalis* activate NLRP3 through extracellular vesicles or caspase-4-mediated pathways, triggering robust inflammatory responses.^{13,14} In contrast, certain commensal bacteria, such as *Bifidobacterium longum* and *Proteus mirabilis*, also induce interleukin (IL)-1 β secretion via NLRP3, but this activation is generally controlled and contributes to immune homeostasis.^{9,15}

Several microbial ligands further modulate this pathway. Lipopolysaccharide, found in Gram-negative bacteria, acts as a priming signal by enhancing the expression of inflammasome-related genes.^{16,17} However, a second signal—commonly ATP released by dying cells—is required for full inflammasome activation, particularly in macrophages.^{18,19} Pore-forming toxins from pathogens, such as *Escherichia coli* also trigger NLRP3 by disrupting ion homeostasis, particularly through potassium efflux.^{20,21}

Together, these signals lead to caspase-1 activation, IL-1 β and IL-18 release, and sometimes pyroptosis. This dual-sensing mechanism enables NLRP3 to mount effective immune responses against pathogens while tolerating commensals, maintaining the balance between protection and overactivation. This bidirectional microbiome–inflammasome loop establishes the foundation for understanding how physiological NLRP3 signaling diverges into pathological activation under dysbiotic conditions.

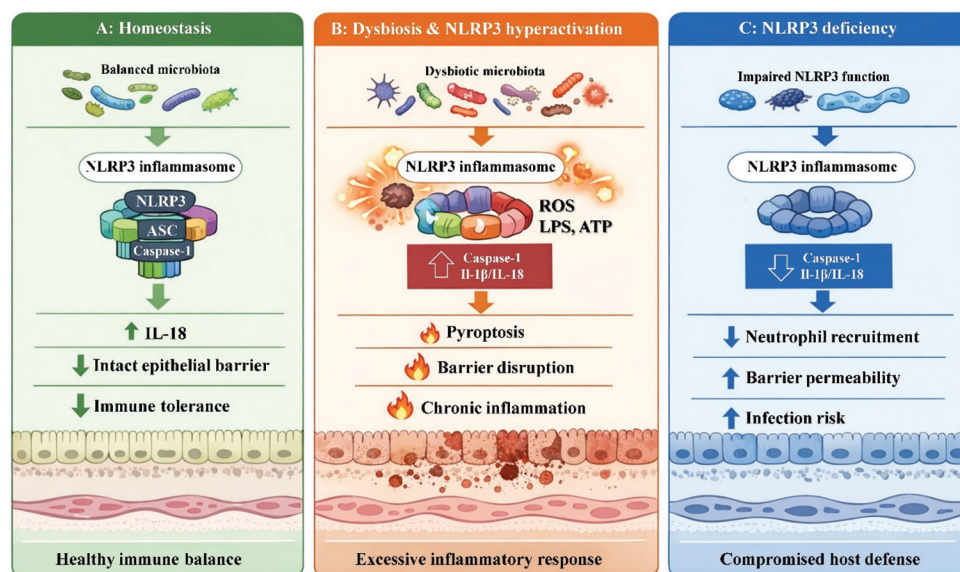


Figure 1. Bidirectional interplay between microbiome dysbiosis and NLRP3 inflammasome activation. (A) Under homeostatic conditions, a balanced microbiome maintains restrained NLRP3 inflammasome activity, supporting epithelial barrier integrity and immune tolerance through tightly regulated cytokine signalling; (B) Microbiome dysbiosis—driven by dietary, environmental, or microbial perturbations—promotes excessive NLRP3 inflammasome activation via microbial products, metabolic stress, mitochondrial dysfunction, and reactive oxygen species, resulting in caspase-1 activation and increased release of IL-1 β and IL-18. This leads to epithelial barrier disruption and sustained inflammatory signaling; (C) Persistent NLRP3 inflammasome activation further alters microbial composition and metabolic outputs, reinforcing dysbiosis and establishing a self-perpetuating inflammatory loop that contributes to disease progression across barrier tissues.

Abbreviations: ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain; ATP: Adenosine triphosphate; Caspase-1: Cysteine-aspartic acid protease-1; IL-1 β : Interleukin-1 beta; IL-18: Interleukin-18; LPS: Lipopolysaccharide; NLRP3: NOD-, LRR- and pyrin domain-containing protein-3; ROS: Reactive oxygen species.

4. Microbial modulation of NLRP3 activity under homeostatic conditions

Under physiological conditions, the gut microbiome plays a central role in calibrating NLRP3 inflammasome activity to maintain immune tolerance and intestinal homeostasis. Rather than driving overt inflammation, commensal bacteria shape inflammasome signaling toward restraint, ensuring effective host defense while preventing excessive immune activation.²² Commensal microbes interact with intestinal epithelial and immune cells to promote balanced immune responses, in part by enhancing anti-inflammatory cytokine networks, such as IL-10, which suppress inappropriate NLRP3 activation and preserve epithelial integrity.^{23,24} In parallel, controlled inflammasome activity in intestinal epithelial cells supports homeostatic IL-18 production, which stimulates mucus secretion from goblet cells and reinforces barrier function, thereby limiting microbial translocation and inflammatory spillover.^{25,26}

Beyond cytokine regulation, specific commensal taxa actively fine-tune inflammasome responsiveness. For example, *Bifidobacterium* species attenuate NLRP3 activation in macrophages, reducing IL-1 β release and preventing unnecessary inflammatory amplification during routine microbial exposure.¹⁵ This selective

dampening of inflammasome signaling underscores how microbial composition, rather than microbial presence alone, determines inflammatory tone.

Emerging evidence further links microbiome homeostasis to mitochondrial regulation of NLRP3. Healthy commensal communities preserve mitochondrial integrity and limit excessive ROS generation, a key upstream signal for aberrant inflammasome activation.^{27,28} Across these coordinated effects on cytokine balance, epithelial defense, and cellular metabolism, the microbiome maintains NLRP3 signaling within a protective, non-pathological range.

Collectively, these mechanisms highlight that restrained NLRP3 activity under homeostatic conditions is not passive, but actively enforced by commensal–host interactions. Disruption of this equilibrium through diet, antibiotics, or chronic stress can destabilize microbial control over inflammasome signaling and shift NLRP3 toward chronic activation, setting the stage for inflammatory disease.

5. Dietary and environmental modulators of the gut microbiome–NLRP3 axis

While host–microbiome interactions maintain restrained NLRP3 activity under physiological conditions, external

modifiers, such as diet, antibiotic exposure, and chronic stress can reshape gut microbial composition and shift inflammasome signaling toward pathological activation. These factors act upstream by altering microbial diversity, epithelial barrier integrity, and metabolic cues, thereby influencing the transition from immune homeostasis to chronic inflammation.

High-fat and Western dietary patterns are consistently associated with dysbiosis characterized by reduced microbial diversity, expansion of Gram-negative taxa, and increased luminal lipopolysaccharide burden. This pro-inflammatory shift promotes intestinal permeability, metabolic endotoxemia, and induces mitochondrial stress, collectively sensitizing NLRP3 inflammasome activation and contributing to obesity, insulin resistance, and systemic low-grade inflammation.^{7,29}

In contrast, fiber-rich diets support the growth of beneficial commensals that produce SCFAs, including butyrate, propionate, and acetate. These metabolites reinforce epithelial barrier integrity, promote regulatory immune programs, and suppress excessive NLRP3 activation, thereby restoring immune tolerance and limiting inflammatory amplification.^{30,31}

Environmental exposures further modulate this axis. Broad-spectrum antibiotics disrupt microbial diversity and deplete SCFA-producing taxa, enhancing epithelial vulnerability and promoting inflammasome activation through increased microbial translocation and inflammatory signaling.³² Similarly, chronic psychological stress alters gut permeability and microbial composition via neuroimmune pathways, linking dysbiosis to systemic and neuroinflammation through NLRP3-dependent mechanisms.³³

Together, dietary composition and environmental exposures emerge as key determinants of gut microbiome structure and NLRP3 inflammasome tone. By shaping microbial ecology and metabolic signaling, these factors influence whether inflammasome activity supports immune homeostasis or drives chronic inflammatory disease.

6. Inflammatory cell death via NLRP3: Balancing host defense and tissue damage

Activation of the NLRP3 inflammasome plays a critical role in early host defense by initiating pyroptosis, a form of programmed inflammatory cell death that limits pathogen replication and amplifies immune signaling. Pyroptosis is triggered in response to pathogen-associated and damage-associated molecular patterns, including bacterial toxins, extracellular ATP, and cellular stress signals,

enabling rapid containment of infection.^{2,34} Downstream of inflammasome activation, caspase-1-dependent cleavage of gasdermin D generates membrane pores that drive cell swelling, lysis, and the release of IL-1 β , IL-18, and intracellular danger signals. This controlled cellular rupture promotes local immune cell recruitment and enhances antimicrobial responses, particularly in infected macrophages.³⁵ Collectively, diverse cellular stress signals converge on inflammasome-mediated cell death pathways to regulate host defense.^{27,36}

While inflammasome-driven pyroptosis is protective during acute infection, sustained or dysregulated NLRP3 activation shifts this response toward pathological tissue injury. In chronic inflammatory settings, including inflammatory bowel disease, persistent pyroptotic signaling contributes to epithelial damage, immune amplification, and disease progression.^{23,37} These observations underscore that pyroptosis represents a double-edged effector mechanism essential for antimicrobial defense but detrimental when uncoupled from appropriate regulatory control.

Collectively, NLRP3-mediated inflammatory cell death must be precisely regulated to balance host protection with tissue preservation. Therapeutic strategies targeting this pathway, therefore, require context-specific modulation rather than blanket suppression, particularly in diseases where chronic inflammasome activation drives pathology.

7. Balancing barrier function: NLRP3's role in epithelial integrity and inflammation

The NLRP3 inflammasome plays a key role in maintaining gut epithelial integrity by regulating immune responses and preserving tight junction structure. Upon activation by microbial signals or cellular stress, NLRP3 promotes the maturation of pro-inflammatory cytokines, such as IL-1 β and IL-18, which are essential for immune surveillance.³⁸ However, excessive or dysregulated activation of NLRP3 can disrupt the epithelial barrier and drive chronic inflammation.

Balanced NLRP3 signaling supports epithelial barrier integrity, whereas dysregulation—often triggered by microbial imbalance or oxidative stress—increases permeability and promotes inflammation.^{30,32,38}

Short-chain fatty acids, beneficial metabolites from gut commensals, can inhibit NLRP3 activation and enhance tight junction protein expression, contributing to mucosal protection.³⁰ In addition, microbe-derived antioxidants activate the Nrf2 pathway, reducing oxidative stress and downregulating the ROS/NLRP3/IL-1 β axis to support epithelial integrity.³⁸

Dysbiosis caused by antibiotics or diet can activate NLRP3 and lead to further barrier disruption, creating a feedback loop of inflammation and tissue damage. In inflammatory bowel disease, loss of NLRP3 function has been linked with increased colonic inflammation and decreased tight junction expression, as shown in NLRP3-deficient mouse models.⁹ Thus, balanced NLRP3 signaling is critical for gut homeostasis, enabling the immune system to tolerate commensals while defending against pathogens.

8. Pathological NLRP3 activation links dysbiosis to chronic disease

Chronic activation of the NLRP3 inflammasome contributes to the pathogenesis of several inflammatory and metabolic diseases by promoting persistent cytokine production and tissue damage. In bacterial vaginosis, microbial dysbiosis—characterized by a decline in *Lactobacillus* species and an increase in anaerobes, such as *Gardnerella vaginalis*—may activate NLRP3, thereby enhancing local inflammation. Although the exact role of NLRP3 in bacterial vaginosis remains unclear, bacterial components have been shown to trigger NLRP3-driven cytokine release, exacerbate inflammation, and increase the risk of infection and adverse reproductive outcomes.^{39–41}

In Crohn's disease, excessive activation of the NLRP3 inflammasome leads to elevated levels of IL-1 β and IL-18, driving chronic intestinal inflammation. Genetic variants affecting NLRP3 function have also been found in some patients, potentially heightening disease susceptibility.^{6,42,43}

Metabolic disorders, such as obesity, type 2 diabetes, and atherosclerosis are similarly influenced by NLRP3 activity. Metabolic stressors, including free fatty acids and glucose, activate the inflammasome, triggering low-grade inflammation that impairs insulin signaling and promotes insulin resistance.^{29,44} In atherosclerosis, NLRP3 activation contributes to plaque development and instability.⁴⁵

Collectively, these findings suggest that targeting NLRP3 may offer a promising therapeutic avenue for managing chronic inflammation in both metabolic and immune-mediated diseases.

9. Skin microbiome–NLRP3 axis: Barrier immunity and chronic inflammation

The skin is the body's largest immunological interface and hosts a specialized microbiome that actively contributes to epithelial integrity and immune homeostasis. Beyond serving as a physical barrier, skin tissues integrate microbial signals through epithelial and immune sensing pathways to regulate inflammatory tone. Disruption of this equilibrium, termed skin dysbiosis, has emerged

as a key driver of chronic inflammatory skin diseases, with aberrant NLRP3 inflammasome activation linking microbial imbalance to barrier dysfunction and persistent inflammation.^{46,47}

Under homeostatic conditions, resident skin commensals, particularly *Staphylococcus epidermidis*, support immune tolerance by modulating keratinocyte responses, promoting antimicrobial peptide production, and limiting excessive inflammasome activation. This controlled host–microbe interaction enables effective pathogen surveillance while preventing chronic inflammation.⁴⁶ In contrast, dysbiosis characterized by reduced microbial diversity and dominance of *S. aureus* is a hallmark of inflammatory skin disorders, such as atopic dermatitis and psoriasis, where disease severity correlates with barrier disruption and heightened inflammatory signaling.^{48,49}

Keratinocytes and skin-resident immune cells express functional inflammasome components and directly respond to microbial and environmental danger signals. Sustained NLRP3 activation in inflammatory lesions reinforces IL-1 β -driven cytokine networks, impairs barrier repair, and promotes chronic inflammation rather than transient antimicrobial defense.^{47,50} Mechanistically, persistent *S. aureus* colonization, including biofilm formation and extracellular vesicle release, can directly activate the NLRP3 inflammasome, establishing a feed-forward loop between microbial persistence, epithelial injury, and immune dysregulation.^{11,48}

Once barrier integrity is compromised, increased antigen penetration and mechanical stress further sensitize inflammasome signaling, accelerating disease progression. This reciprocal interaction between microbial imbalance and epithelial dysfunction mirrors the gut microbiome–NLRP3 axis described earlier, highlighting a conserved inflammatory principle across barrier tissues.

From a therapeutic perspective, recognition of the skin microbiome–NLRP3 axis reframes chronic inflammatory skin diseases as disorders of immune–microbial miscommunication rather than isolated immune pathology. Emerging strategies aimed at restoring microbial balance or selectively modulating inflammasome activity offer the potential to recalibrate inflammation without broadly suppressing host defense.⁵¹

10. Consequences of NLRP3 deficiency: Compromised immunity and infection susceptibility

In contrast to pathological hyperactivation, loss of NLRP3 function also carries significant immunological

consequences, particularly by weakening host defense against infections. The NLRP3 inflammasome is a central component of innate immunity, enabling effective detection of microbial danger signals and initiation of inflammatory responses. When this pathway is compromised, the capacity to mount timely and coordinated immune reactions is markedly reduced, increasing susceptibility to infection.

Mechanistically, NLRP3 is required for caspase-1 activation and subsequent maturation of the pro-inflammatory cytokines IL-1 β and IL-18, both of which are essential for early immune orchestration. NLRP3-deficient mice exhibit substantially reduced IL-1 β production following infection, resulting in impaired recruitment of immune cells to sites of pathogen invasion and allowing unchecked microbial proliferation.⁵²

Neutrophils, among the earliest responders during infection, are particularly affected by this deficiency. Reduced IL-1 β and IL-18 signaling leads to defective neutrophil chemotaxis and diminished phagocytic capacity, compromising bacterial clearance. This phenomenon has been observed in inflammatory bowel disease models, where intact NLRP3 signaling is required for effective neutrophil-mediated defense.^{23,25}

Beyond immune cell recruitment, NLRP3 also contributes to epithelial barrier integrity. Loss of NLRP3 activity disrupts tight junction organization, increases epithelial permeability, and facilitates microbial translocation across barrier surfaces.^{24,53} Such barrier failure not only promotes local inflammation but also increases the risk of systemic infection.

Importantly, NLRP3 deficiency affects adaptive immunity as well. NLRP3 signaling supports T helper 1 cell differentiation, a critical component of host defense against intracellular pathogens. Impaired NLRP3 function leads to reduced interferon- γ production and diminished activation of macrophages and cytotoxic T cells, further weakening antimicrobial immunity.⁵⁴

Consistent with these mechanistic insights, NLRP3-deficient mice display heightened susceptibility to enteric pathogens, such as *Citrobacter rodentium*, resulting in increased pathogen burden and more severe disease outcomes.⁵² Together, these findings underscore that both excessive activation and insufficient function of NLRP3 disrupt immune homeostasis, highlighting the necessity for tightly regulated inflammasome activity to maintain effective host defense.

11. Concluding remarks and future directions

Understanding the interplay between the NLRP3 inflammasome and dysbiosis opens exciting avenues for further research and therapeutic innovation. While existing studies have established a strong link between microbiome imbalances and NLRP3 activation, future investigations should focus on uncovering the precise molecular mechanisms driving this interaction across diverse biological systems, including the gut, reproductive tract, and central nervous system.

One critical aspect of future research is the identification of robust biomarkers that can reliably indicate dysbiosis-induced inflammasome activation. This would enable early disease detection and the development of targeted interventions. In addition, expanding our knowledge of microbial metabolites that regulate NLRP3 activity may facilitate the design of microbiome-based therapeutics, such as next-generation probiotics or engineered microbiota capable of modulating inflammasome responses.

From a clinical perspective, continued exploration of novel NLRP3 inhibitors and microbiome-modulating strategies holds promise for reducing chronic inflammation and preventing disease progression. Precision medicine approaches leveraging host-microbiome interactions could lead to tailored therapies for inflammatory and metabolic diseases. Furthermore, examining the role of dietary and lifestyle factors in shaping the NLRP3-microbiome axis may yield new strategies for non-pharmacological interventions.

Finally, interdisciplinary collaborations between microbiologists, immunologists, and bioinformaticians will be essential to integrate multi-omics data and construct comprehensive models of NLRP3-mediated inflammation. The ultimate goal is to translate these findings into innovative therapies that restore immune balance and improve health outcomes.

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Conflict of interest

Atar Singh Kushwah serves as the Youth Editorial Board Member of this journal but was not involved, directly or indirectly, in the editorial decision-making and peer-review process for this paper. All other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Atar Singh Kushwah

Visualization: Atar Singh Kushwah, Shishir Singh

Writing – original draft: Shishir Singh

Writing – review & editing: Rajeev Nema, Monisha Banerjee, Atar Singh Kushwah

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Not applicable.

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