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REVIEW ARTICLE

NOD-like receptor pyrin domain-containing protein 3 inflammasome activation in microbiota-induced neuroinflammation: Relevance to autism and stress disorders

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Abstract

The gut–brain axis has evolved into a bidirectional neuroimmune communication network linking microbial ecology, innate immunity, endocrine signaling, and central nervous system function. The NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome is a key cytosolic sensor that converts signals from microbes into pro-inflammatory pathways. Growing evidence shows that changes in microbial metabolites, intestinal permeability, and systemic immune activation caused by dysbiosis all lead to NLRP3 inflammasome signaling in microglia, astrocytes, and neurons. This neuroinflammatory response mediated by the inflammasome has been progressively associated with the pathophysiology of autism spectrum disorder (ASD) and stress-related neuropsychiatric diseases, such as anxiety and post-traumatic stress disorder. Gut microbial disturbances facilitate peripheral cytokine release, compromise the blood–brain barrier, induce mitochondrial stress, and generate reactive oxygen species—all of which are crucial upstream activators of NLRP3. The development of interleukin (IL)-1β and IL-18, which depends on inflammasomes, worsens synaptic plasticity, neurotransmitter balance, and control of the hypothalamic–pituitary–adrenal axis. In this review, we integrate novel mechanistic findings that link gut microbiota dysregulation to NLRP3-mediated neuroinflammation, clarify its involvement in ASD and stress susceptibility, and examine treatment approaches targeting microbial modulation and inflammasome suppression. Comprehending this immunometabolic axis may facilitate targeted neuroimmune therapies for neurodevelopmental and stress-related diseases.

Keywords: NOD-like receptor pyrin domain-containing protein 3 inflammasome; Dysbiosis; Autism spectrum disorder; Stress disorder; Neuroinflammation; Microglia; Interleukin-1 beta; Interleukin-18

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1. Introduction

Neurodevelopmental and stress-related disorders are increasingly viewed as complex conditions characterized by immune–neural interface dysfunction, rather than just neurotransmitter imbalances.[1-3] While initial explanations focused on anomalies in monoaminergic signaling, recent findings emphasize ongoing low-grade inflammation, dysregulated innate immune responses, and compromised neuroimmune

communication as the primary causes.[4,5] Autism spectrum disorder (ASD), anxiety disorders, and post-traumatic stress disorder reliably show immune system changes both peripherally and centrally.[3,6] These factors include increased pro-inflammatory cytokine levels in the blood, microglial activation, changes in T cell polarization, and alterations in gut microbial composition.[7,8] In ASD, both clinical and preclinical research has found elevated levels of interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor alpha, along with microglial priming in cortical and limbic areas.[6,9] Similarly, ongoing stress results in the continuous activation of innate immune pathways, such as nuclear factor kappa B (NF-κB)–dependent transcription, leading to persistent neuroinflammation.[5,10] These findings have broadened the disease model to encompass not only synaptic function and neurotransmitters but also immune signaling, metabolic stress, and environmental influences.[2,4] At the molecular level, the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome is essential for innate immunity, connecting external immune cues to brain inflammation.[3,11] The NLRP3 inflammasome is a cytosolic innate immune sensor that transduces microbial, metabolic and cellular stress signals into inflammatory responses. By regulating IL-1β and IL-18 maturation, NLRP3 serves as a key interface between peripheral immune activation and neuroinflammatory processes. The molecular architecture and activation mechanisms of the inflammasome are discussed in detail in Section 2, and a general overview is provided here.

The gut microbiota also plays a key role as an upstream regulator of immune balance in both the body and brain.[8,12] Microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids, indole derivatives, and other tryptophan metabolites, serve as vital signaling mediators that influence epithelial barrier integrity, immune cell development, and neurochemical stability.[12] For example, SCFAs modulate histone deacetylase (HDAC) activity, promote regulatory T cell growth, and reduce excessive inflammatory signaling.[12] Metabolites derived from tryptophan modulate aryl hydrocarbon receptor (AhR) pathways, thereby influencing microglial activity and the integrity of the blood–brain barrier.[8] In ASD, gastrointestinal issues often occur before or along with behavioral symptoms.[7] This indicates that initial changes in the gut microbiome could activate inflammasome pathways during critical stages of neurodevelopment.[12] Research using maternal immune activation models indicates that inflammatory signals during pregnancy can modify microglial development, affect synaptic pruning, and influence the development of social behavior in offspring.[13] These effects are increasingly linked to cytokine signaling that depends on inflammasomes.[3] Chronic stress paradigms also show that NLRP3 expression is higher in the hippocampus and amygdala, and this is linked to behaviors that resemble anxiety and depression.[5,10] These findings collectively highlight the NLRP3 inflammasome as a key molecular hub connecting microbial signals, metabolic stress, and neuroimmune disturbances.[3,11] NLRP3 operates within an immunometabolic network that links gut health, barrier function, mitochondrial integrity, and synaptic changes, rather than functioning as an isolated inflammatory factor.[12] Persistent activation within this network may reflect a common process underlying susceptibility in neurodevelopment and stress-related disorders.[10] This review combines modern mechanistic evidence showing how microbiota-driven signals activate the NLRP3 inflammasome and highlights this pathway's role in ASD and neuropsychiatric stress-related conditions. By integrating microbial ecology, innate immune signaling, and neurology, we aim to explore new treatment strategies targeting the microbiota–inflammasome brain axis.

2. Molecular architecture and regulatory control of the NOD-like receptor family pyrin domain-containing 3 inflammasome

The NLRP3 inflammasome is a multiprotein signaling complex found in the cytosol, part of the receptor family, and distinguished by its nucleotide-binding domain and leucine-rich repeats.[11,14] It plays a vital role in triggering innate immune responses when stress or danger signals are detected.[15] The complex includes an N-terminal pyrin domain (PYD), a central NACHT domain with adenosine triphosphatase (ATPase) activity, and a C-terminal leucine-rich repeat (LRR) region.[11] The PYD assists in homotypic protein interactions and recruits the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), which has a caspase recruitment domain.[14] The NACHT domain is crucial for ATP-driven changes in shape and oligomer formation, which are vital in inflammasome assembly.[15] Inhibiting its ATPase activity blocks this process, highlighting its essential role in activation.[16] Although the precise sensing function of the LRR domain remains unclear, it likely assists in autoregulatory folding and maintaining structural integrity, thus avoiding unintended activation when the cell is inactive.[11] During activation, the NACHT domain of NLRP3 facilitates self-oligomerization, creating a scaffold that attracts ASC through PYD–PYD interactions. This process results in filament formation and speck assembly.[14] Subsequently, ASC binds pro-caspase-1 through caspase recruitment domain–caspase recruitment domain interactions, culminating in the formation of the mature inflammasome complex.[17] Autocatalytic cleavage of caspase-1, induced by proximity, activates it, allowing

it to process pro-IL-1β and pro-IL-18 into their mature cytokines, and to cleave gasdermin D, which triggers membrane pore formation and pyroptotic cell death.[18] Within the central nervous system (CNS), this molecular machinery is primarily operational in microglia and astrocytes, although neurons may express inflammasome components under pathological conditions. The assembly process is highly sensitive to ionic imbalances, mitochondrial dysfunction, and metabolic disturbances, all of which are common in neuroinflammatory conditions.[3] The activation of the NLRP3 inflammasome occurs through a precisely controlled two-step process: priming then activation (Figure 1).[11] This regulation ensures the inflammasome forms only when real cellular stress is present. The priming phase involves transcriptional regulation and is typically triggered by pattern-recognition receptors, such as Toll-like receptors (TLRs) or cytokine receptors.[14] For instance, stimulation of TLR4 by lipopolysaccharide or activation of receptors by tumor necrosis factor and IL-1 activates NF-κB signaling, which causes it to move into the nucleus and upregulate the transcription of NLRP3, pro-IL-1β, and pro-IL-18. In addition to transcriptional induction, priming initiates crucial post-translational modifications that "license" NLRP3 for activation by affecting its stability, conformation, and subcellular localization important factors.[15] Importantly, priming by itself does not trigger inflammasome assembly; instead, it creates a molecular environment that makes secondary activation signals more likely.[11] In the CNS, microglial priming can happen due to circulating cytokines, microbial metabolites, or stress-related changes in glucocorticoids.[19] Chronic priming states are particularly important in neurodevelopmental and stress-related conditions, which often involve persistent NF-κB activation and heightened inflammatory responses. The activation phase begins not with detecting a single ligand but by sensing disruptions in cellular homeostasis.[10] A drop in intracellular potassium usually triggers NLRP3 activation. Stimuli such as extracellular ATP activating P2X7 receptors cause potassium to exit the cell, thereby enabling conformational changes that promote oligomerization.[20] Mitochondrial dysfunction plays a key role in inflammasome activation by mechanisms such as increased production of mitochondrial reactive oxygen species, the release of oxidized mitochondrial DNA, and exposure of cardiolipin. These processes collectively facilitate the assembly of the inflammasome.[21] Oxidized mitochondrial DNA can directly bind to NLRP3, boosting its activation, especially in microglia, where mitochondrial stress is linked to chronic neuroinflammation.[3] Furthermore, lysosomal rupture after engulfing particulates or crystals releases cathepsins into the cytoplasm, acting as additional triggers.[22] Although initially studied in peripheral macrophages, this lysosomal stress response may also occur in microglia when they respond to aggregated proteins. Recent research indicates that the movement of chloride and calcium ions influences activation, implying that NLRP3 functions more as a sensor of ionic imbalance rather than a receptor for specific molecular motifs.[3] Multiple upstream signals induce NACHT-driven oligomerization, which subsequently recruits ASC and activates caspase-1.[14] Due to NLRP3's role in causing substantial inflammation, its activity is tightly regulated by various post-translational mechanisms.[11] Ubiquitination is an important post-translational regulatory mechanism of NLRP3 stability and activation. K48-linked ubiquitination generally promotes NLRP3 proteasomal degradation and inhibits inflammasome activation, whereas K63-linked ubiquitination promotes inflammasome assembly and signaling. During the priming phase, deubiquitinases such as BRCA1/BRCA2-containing complex subunit 3 can remove inhibitory K48-linked ubiquitin chains, thereby stabilizing NLRP3 and increasing its sensitivity to stimulation signals.[14] Phosphorylation then modifies inflammasome sensitivity by altering its structure and mobility within the cell.[11] Some kinases promote inflammasome formation, while others serve as brakes, linking stress-response pathways like mitogen-activated protein kinase cascades to the regulation of inflammasome activity.[15] A critical structural licensing factor in the activation phase is NIMA-related kinase 7, a serine/threonine kinase that binds to the NACHT and LRR domains of NLRP3, stabilizing its oligomerized conformation and permitting inflammasome assembly.[23] Notably, NIMA-related kinase 7 is dispensable during priming but essential during activation, providing an additional layer of regulation that links inflammasome assembly to cell cycle-independent stress signaling.[18] Priming, activation signals, and post-translational processes collectively ensure that inflammasome activity occurs only under suitable conditions.[11] However, in chronic inflammatory states such as ongoing gut dysbiosis, metabolic stress, or extended psychological stress, these regulatory systems can fail.[24] Persistent NF-κB activation boosts priming, while mitochondrial dysfunction raises reactive oxygen species levels.[19] Additionally, decreased ubiquitin-mediated degradation lowers the activation threshold, all of which amplify inflammasome sensitivity.[14] This results in excessive production of IL-1β and IL-18 and heightened pyroptosis.[18] Activation of the CNS leads to hyperactive microglia, disrupted synaptic plasticity, an imbalance between excitatory and inhibitory signals, and damage to the blood–brain barrier.[3] These phenomena demonstrate how abnormal NLRP3 signaling links peripheral immune dysfunction with central

neuroinflammation, connecting microbial signals, stress responses, and the risk of neurodevelopmental disorders.[10] The structural organization of NLRP3 and the canonical two-step activation process are summarized in Figure 1.

3. Gut microbiota as upstream modulators of NOD-like receptor family pyrin domain-containing 3 signaling

The gut microbiota forms a dynamic ecological system whose metabolic and structural integrity significantly impacts host innate immune signals.[25] There is growing evidence that changes in microbial composition and metabolite production are upstream regulators of NLRP3 inflammasome activation.[26,27] This links gut balance to systemic and central inflammatory states.[28] Dysbiosis, caused by factors such as age, long-term psychological stress, an unbalanced diet, an infection, or exposure to antibiotics, disrupts the functional balance of the intestinal milieu and sets off a chain of events that readies and activates inflammasome pathways (Figure 2).[10] A characteristic feature of dysbiosis is a reduction in beneficial commensal bacteria, especially butyrate-producing species such as *Faecalibacterium* and

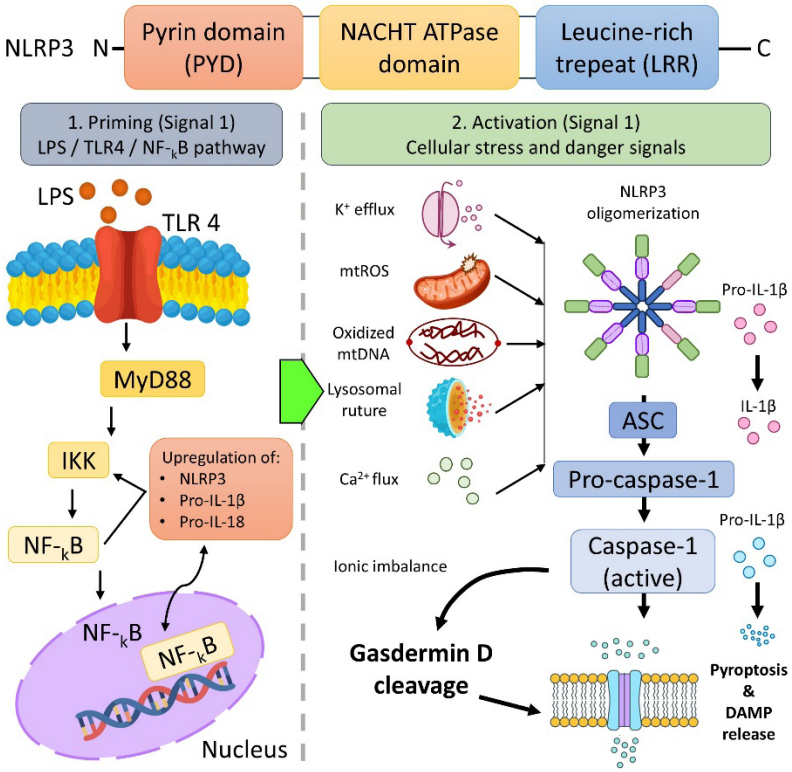

Figure 1. Structural organization and canonical two-step activation pathway of the NLRP3 inflammasome. Schematic representation of the structural domains and canonical two-step activation process of the NLRP3 inflammasome. The NLRP3 protein consists of an N-terminal pyrin domain (PYD), a central NACHT ATPase domain responsible for oligomerization, and a C-terminal leucine-rich repeat (LRR) domain involved in autoregulation and stress sensing. Inflammasome activation requires two sequential signals. Signal 1 (Priming) is initiated by microbial products such as lipopolysaccharide (LPS), which activate Toll-like receptor 4 (TLR4) and downstream MyD88–IKK–NF-κB signaling, resulting in transcriptional upregulation of *NLRP3*, *pro-IL-1β*, and *pro-IL-18*. Signal 2 (Activation) is triggered by diverse cellular stress and danger-associated signals, including potassium (K^+) efflux, mitochondrial reactive oxygen species (mtROS) generation, oxidized mitochondrial DNA (mtDNA) release, lysosomal rupture, calcium (Ca^{2+}) flux, and ionic imbalance. These signals promote NLRP3 oligomerization and recruitment of the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC), leading to the assembly of the inflammasome complex and activation of pro-caspase-1. Active caspase-1 subsequently cleaves pro-IL-1β and pro-IL-18 into their mature inflammatory cytokines and processes gasdermin D, resulting in membrane pore formation, pyroptotic cell death, and the release of danger-associated molecular patterns (DAMPs). Collectively, these events position the NLRP3 inflammasome as a critical molecular sensor linking microbial stimuli and cellular stress to innate immune activation and neuroinflammatory responses. Created using Microsoft PowerPoint.
Abbreviations: CARD: Caspase recruitment domain; IKK: Inhibitor of nuclear factor kappa B kinase; IL: Interleukin; MyD88: Myeloid differentiation primary response 88; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain-containing protein 3.

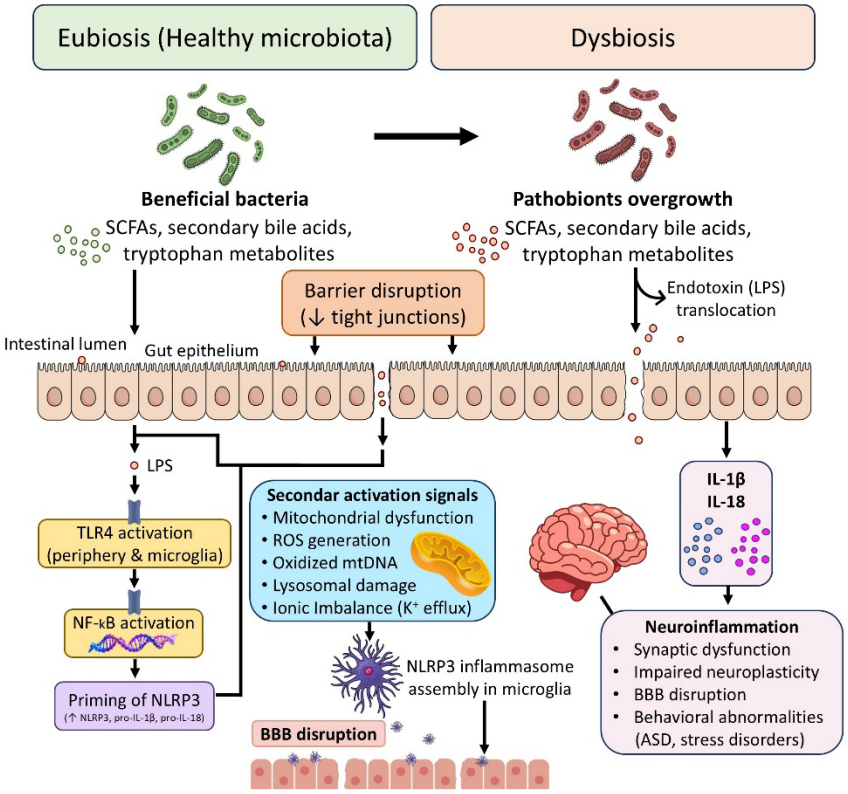

Figure 2. Gut microbiota dysbiosis promotes NLRP3 inflammasome activation and neuroinflammation through the gut–brain axis. Schematic illustration of the mechanisms by which gut microbial dysbiosis promotes NLRP3 inflammasome activation and neuroinflammation through the gut–brain axis. Under physiological conditions (eubiosis), beneficial gut microbiota produce immunoregulatory metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan-derived metabolites, which maintain intestinal barrier integrity, support immune homeostasis, and suppress excessive inflammatory signaling. In contrast, dysbiosis is characterized by reduced beneficial microbial populations and expansion of pathobionts, leading to decreased production of protective microbial metabolites and disruption of intestinal tight junctions. Increased intestinal permeability facilitates the translocation of bacterial endotoxins, such as lipopolysaccharide (LPS), into the circulation, where they activate Toll-like receptor 4 (TLR4) signaling in peripheral immune cells and microglia. Subsequent activation of the NF-κB pathway induces transcriptional priming of *NLRP3*, *pro-IL-1β*, and *pro-IL-18*. Simultaneously, dysbiosis-associated cellular stress promotes secondary activation signals, including mitochondrial dysfunction, reactive oxygen species (ROS) generation, release of oxidized mitochondrial DNA (mtDNA), lysosomal damage, and ionic imbalance, particularly potassium (K^+) efflux. These convergent signals trigger assembly of the NLRP3 inflammasome in microglia, resulting in caspase-1 activation and maturation of the pro-inflammatory cytokines IL-1β and IL-18. Sustained inflammasome activation contributes to blood–brain barrier (BBB) disruption, chronic neuroinflammation, impaired synaptic plasticity, altered neurodevelopmental processes, and behavioral abnormalities associated with autism spectrum disorder (ASD) and stress-related disorders. Created using Microsoft PowerPoint.
Abbreviations: IL: Interleukin; NF-κB: Nuclear factor kappa B; NLRP3: NLR family pyrin domain-containing protein 3.

Roseburia.[29,30] This decrease leads to lower production of SCFAs, which are crucial for maintaining a healthy epithelial barrier, supporting immune tolerance, and regulating inflammation.[31,32] When SCFA levels decrease, the synthesis of tight junction proteins such as claudins and occludin declines, resulting in increased intestinal permeability.[33] This weakened barrier allows microbial components, especially lipopolysaccharide, to enter the bloodstream more readily, often causing metabolic endotoxemia.[34] Once in circulation, lipopolysaccharide interacts with TLR4 on immune cells, activating NF-κB-dependent pathways that boost the production of NLRP3 and pro-IL-1β.[27] This provides the priming signal necessary for inflammasome assembly. Thus, barrier disruption not only reflects localized intestinal issues but also enhances systemic inflammasome activation.

In addition to maintaining barrier integrity, microbial metabolites directly modulate inflammasome activity at the cellular level.[26] In physiological conditions, SCFAs, such as acetate, propionate, and butyrate, mainly exert anti-inflammatory effects by inhibiting histone HDACs, activating G-protein-coupled receptors like GPR41 and

GPR43, and inducing regulatory T cell differentiation; however, certain pro-inflammatory effects have been reported depending on their concentration, tissue environment, and cell type.[31,35] Butyrate's HDAC inhibition enhances histone acetylation at anti-inflammatory gene promoters and diminishes pro-inflammatory mediators, thereby suppressing NF-κB signaling.[32] Furthermore, SCFA signaling via GPR43 affects neutrophil recruitment and macrophage activation, indirectly modulating inflammasome priming.[35] Experimental evidence indicates that restoring SCFA levels reduces excessive IL-1β production and NLRP3 activation,[26,35] implying that a microbial metabolite deficiency lowers the inflammasome's activation threshold. In contrast, aging or stress-induced dysbiosis shifts microbial metabolism toward pro-inflammatory profiles, decreasing SCFA production and heightening the risk of inflammasome hyperactivation.[34]

Variations in bile acid breakdown highlight the complex relationship between microbiota and the inflammasome.[12] Microbial enzymes convert primary bile acids into secondary bile acids, which serve as signaling molecules via the farnesoid X receptor and TGR5, both of which modulate inflammatory pathways. Disruption of bile acid homeostasis has been shown to influence NLRP3 inflammasome activation, in part by altering mitochondrial activity and reactive oxygen species production.[27] Beneficial bacteria generate indole metabolites from tryptophan that trigger the AhR, which is crucial for maintaining the epithelial barrier and immune tolerance.[36] Disruption of these pathways undermines mucosal defenses and increases the risk of inflammation. Microbiota-driven inflammasome activation influences peripheral immune responses and the inflammation within the CNS. Dysbiosis affects inflammasome signaling via various metabolic pathways that promote anti-inflammatory responses, rather than relying on a single mechanism. Mechanistic insights into the regulation of NLRP3 inflammasome activity by microbiota-derived metabolites have been further identified. Canonical SCFAs have emerged as key regulators of inflammasome signaling, alongside altered microbiota tryptophan metabolism, bile acid conversion, and AhR ligands. Recent studies have shown that microbiota-dependent AhR activation inhibits oxidative stress and NLRP3 activation by coordinating modulation of host metabolic pathways and immune responses. Metabolite-mediated regulation of mitochondrial redox homeostasis is a key mechanism linking microbial ecology to inflammasome regulation, as demonstrated by growing evidence.[12] Together, these results support the notion that microbial metabolites are not just biomarkers of dysbiosis but potent regulators of NLRP3-dependent neuroimmune signaling. Recent mechanistic studies demonstrate that microbiome-derived metabolites regulate host physiology not only via anti-inflammatory functions but also through other mechanisms.[25,26,31] Microbial metabolites have increasingly been shown to regulate the host inflammatory response and directly modulate NLRP3 inflammasome activation via integrated signaling networks that govern immune cell differentiation, mitochondrial metabolism, epithelial barrier integrity, and neuroimmune communication by modulating oxidative stress, cellular metabolism, and innate immune signaling pathways.[26,27,31,36,37] These studies position microbiota-derived metabolites as active regulators of host immunometabolic homeostasis and establish a mechanistic link among microbial ecology, neuroinflammation, and brain function.

Microbiota-driven inflammasome activation influences peripheral immune responses and the inflammation within the CNS. Cytokines like IL-1β and IL-6, generated during peripheral inflammasome activation, reach the brain through several pathways: crossing damaged blood–brain barrier areas,[28,38] prompting endothelial cells to emit inflammatory signals, or activating vagal afferent nerves that carry immune messages to the brainstem.[39,40] In the CNS, these cytokines increase local NLRP3 expression and prepare microglia for activation.[25] When the body's immune response is active, microglia become more sensitive to secondary triggers such as mitochondrial stress and ionic flux, potentially leading to inflammasome formation.[35] In chronic states such as ongoing psychological stress or dysbiosis, this immune communication between the periphery and the brain perpetuates a cycle of continuous inflammation. During this cycle, signals from the gut elevate microglial activation, while neuroinflammation further impairs the regulation of the hypothalamic–pituitary–adrenal (HPA) axis.[39,40]

These findings emphasize the essential role of gut microbiota in controlling NLRP3 inflammasome activity. Barrier damage associated with dysbiosis primes inflammation through endotoxin-induced NF-κB activation,[34] while alterations in microbial metabolites affect mitochondrial stress, oxidative balance, and immune cell differentiation, all of which influence activation.[26,27] Including peripheral signals in central immune pathways underscores the molecular link between gut ecology and neuroinflammatory diseases. These interconnected pathways linking gut microbial dysbiosis to NLRP3 activation and neuroinflammation are illustrated in Figure 2. The microbiota not only responds to disease but also actively influences inflammasome responses, impacting the risk of neurodevelopmental and stress-related

disorders. To develop personalized treatments that restore microbial balance and control inflammasome activity in both peripheral and central regions, understanding this complex regulation is essential. The major upstream activators and regulatory signals involved in NLRP3 inflammasome activation in ASD and stress-related disorders are summarized in Table 1.

4. Common mechanisms linking the inflammasome to neurobehavioral dysfunction

The shared and disorder-specific mechanisms linking NLRP3 inflammasome activation to ASD and stress-related disorders are summarized in Figure 3. NLRP3 inflammasome activation facilitates neurobehavioral dysfunction through multiple mechanisms shared by ASDs and stress-related disorders. One major downstream consequence is the caspase-1-dependent maturation of IL-1β and IL-18, which can sustain microglial activation and enhance neuroinflammatory signaling. Chronic IL-1β exposure may interfere with synaptic plasticity by reducing long-term potentiation, destabilizing dendritic spines, and disrupting neurotrophic signaling pathways. In particular, IL-1β-induced suppression of brain-derived neurotrophic factor (BDNF) may impair synaptic maturation, neuronal resilience, and adaptive circuit remodeling. In addition to modulating synapses, cytokine signaling arising from inflammasome activation can disrupt the balance between excitatory and inhibitory neurotransmission, contributing to aberrant circuit function. These effects have relevance to neurodevelopmental disruption in ASD and maladaptive stress responses in stress-related disorders. NLRP3 activation is also strongly associated with mitochondrial dysfunction and oxidative stress, which provide secondary activation signals and sustain a self-amplifying inflammatory cycle. Damaged mitochondria generate reactive oxygen species and oxidized mitochondrial DNA, both of which contribute to inflammasome assembly and cytokine release. Another common mechanism is the dysregulation of neuroendocrine feedback. IL-1β and other inflammatory mediators can interfere with glucocorticoid

Table 1. Major upstream activators of the NLRP3 inflammasome and their relevance in autism spectrum disorder and stress-related disorders

Activator/Signal	Source	Mechanism of NLRP3 activation	Relevance to ASD/stress disorders	Key references
Lipopolysaccharide	Microbial	Activates TLR4/NF-κB priming pathway	Increased gut permeability and endotoxemia reported in ASD	41,42
Extracellular ATP	Host-derived danger signal	Activates P2X7 receptor causing K^+ efflux	Promotes microglial inflammasome activation under chronic stress	20
K^+ efflux	Host cellular stress	Drives NLRP3 conformational activation and oligomerization	Common downstream activation signal in neuroinflammation	20
Mitochondrial ROS	Host mitochondrial dysfunction	Induces oxidative stress-mediated inflammasome assembly	Elevated oxidative stress in ASD and chronic stress models	21,43
Oxidized mtDNA	Host mitochondrial damage	Directly binds and activates NLRP3	Associated with persistent microglial activation	21
Lysosomal rupture	Host cellular stress	Releases cathepsins into cytosol	Contributes to inflammasome activation in activated microglia	22
SCFA deficiency	Microbial dysbiosis	Reduces anti-inflammatory signaling and increases NF-κB activation	Reduced butyrate-producing bacteria observed in ASD	7,32
Altered bile acid metabolism	Microbial dysbiosis	Disrupts FXR/TGR5-mediated anti-inflammatory signaling	Promotes oxidative stress and inflammasome sensitivity	27
Reduced tryptophan metabolites	Microbial dysbiosis	Impairs AhR-mediated immune regulation	Associated with impaired gut barrier and neuroimmune signaling	36
Chronic psychological stress	Host neuroendocrine stress	Enhances NF-κB priming and ROS production	Drives HPA axis dysregulation and neuroinflammation	44,45

Abbreviations: AhR: Aryl hydrocarbon receptor; ASD: Autism spectrum disorder; FXR: Farnesoid X receptor; HPA: Hypothalamic–pituitary–adrenal; mtDNA: Mitochondrial DNA; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; TLR4: Toll-like receptor 4.

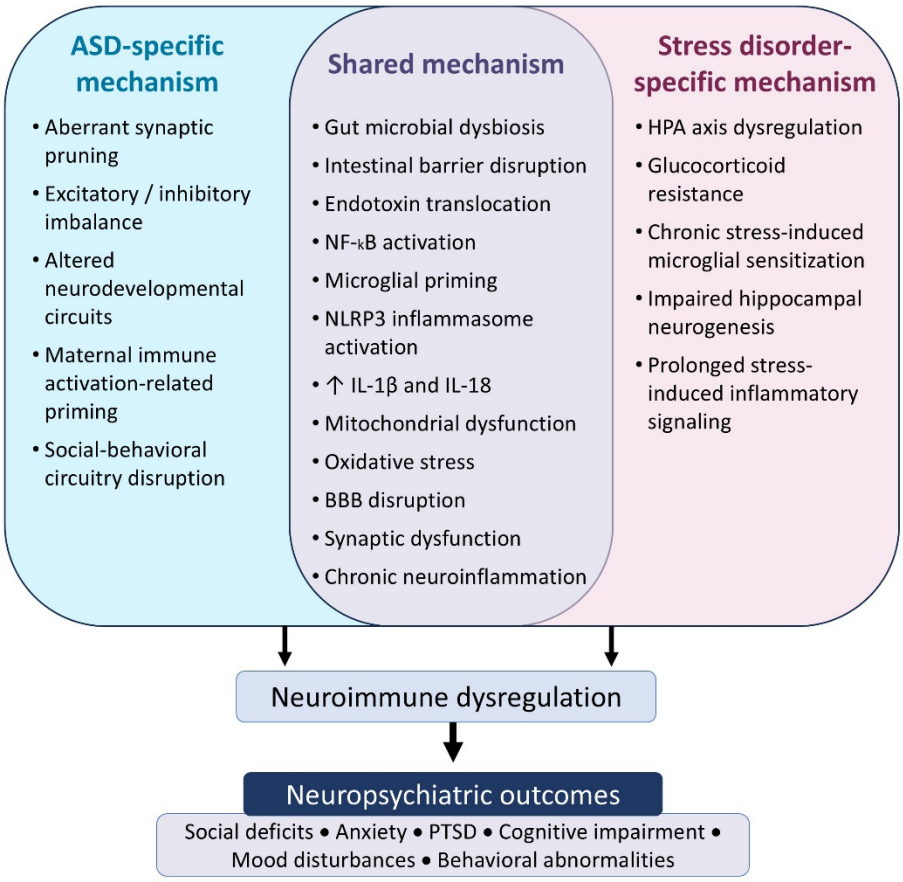

Figure 3. Shared and distinct NLRP3 inflammasome-associated pathways in autism spectrum disorder and stress-related disorders. Comparative overview of shared and disorder-specific NLRP3 inflammasome-related mechanisms in autism spectrum disorder (ASD) and stress-related disorders. Common pathways include gut microbial dysbiosis, intestinal barrier disruption, endotoxin translocation, NF-κB activation, microglial priming, NLRP3 inflammasome activation, increased production of IL-1β and IL-18, mitochondrial dysfunction, oxidative stress, BBB disruption, synaptic dysfunction, and chronic neuroinflammation. ASD-specific mechanisms involve aberrant synaptic pruning, excitation–inhibition imbalance, altered neurodevelopmental circuitry, maternal immune activation-related priming, and social-behavioral circuit disruption. Stress-related disorder-specific mechanisms include HPA axis dysregulation, glucocorticoid resistance, chronic stress-induced microglial sensitization, impaired hippocampal neurogenesis, and prolonged inflammatory signaling. These pathways converge on neuroimmune dysregulation, leading to neuropsychiatric manifestations such as social deficits, anxiety, PTSD, cognitive impairment, mood disturbances, and behavioral abnormalities. Created using Microsoft PowerPoint.
Abbreviations: BBB: Blood–brain barrier; HPA: Hypothalamic–pituitary–adrenal; IL: Interleukin; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like receptor family pyrin domain-containing protein 3; PTSD: Post-traumatic stress disorder.

receptor signaling and impair negative feedback regulation of the HPA axis.[46] This can lead to prolonged inflammation and increased vulnerability to stress-related behavioral abnormalities. Thus, impaired synaptic plasticity, deficient BDNF signaling, mitochondrial stress, microglial priming, blood–brain barrier dysfunction, and dysregulation of the HPA axis are common pathways through which NLRP3 inflammasome activation may contribute to neurobehavioral dysfunction in ASD and stress-related disorders. A comparative overview of these common and disorder-specific pathways is presented in Figure 3.

5. Mechanistic role of NOD-like receptor family pyrin domain-containing 3 inflammasome in autism spectrum disorder

Autism spectrum disorder is increasingly recognized as a neurodevelopmental condition involving complex interactions between gut dysbiosis, immune dysfunction, mitochondrial stress, and abnormal synaptic connectivity. A central mechanistic question is how peripheral microbial disturbances translate into persistent neurodevelopmental and behavioral abnormalities in the brain. Emerging

evidence suggests that the NLRP3 inflammasome may serve as a molecular bridge linking alterations in microbial metabolites, microglial activation, cytokine dysregulation, synaptic dysfunction, and ASD-associated behavioral phenotypes, although direct evidence in human ASD brain tissue remains limited.[47–50]

Research has shown that certain individuals with ASD exhibit higher levels of pro-inflammatory cytokines, including IL-1β and IL-18, suggesting abnormal inflammasome activity.[47] However, not all clinical studies have reported elevated IL-1β or IL-18 levels in ASD, indicating substantial heterogeneity among patient populations and highlighting the need for careful interpretation of inflammasome-associated biomarkers. Since IL-1β and IL-18 are typical products of caspase-1 cleavage following NLRP3 activation, their higher levels strongly suggest inflammasome involvement in ASD-related immune responses.[43,51–55] In addition to central mechanisms, gastrointestinal problems frequently observed in ASD may also enhance peripheral inflammasome activation.[56] Changes in the gut microbiota, increased intestinal permeability, and higher circulating endotoxin levels provide continuous priming signals through TLR4–NF-κB pathways, thereby raising NLRP3 levels in peripheral immune cells and microglia.[41,42] Importantly, depletion of microbiota-derived SCFAs, particularly butyrate, weakens anti-inflammatory signaling mediated through histone deacetylase inhibition and GPR43 activation, thereby enhancing NF-κB-dependent priming of the NLRP3 inflammasome. Simultaneously, reduced tryptophan-derived metabolites impair AhR signaling, further compromising epithelial integrity and microglial immune regulation. Neuropathological research further confirms neuroinflammation in ASD, revealing microglial activation in the cortex, hippocampus, and cerebellum.[9,49] Microglia are the brain's innate immune cells and key players in inflammasome formation within the CNS. Normally, they help with synaptic remodeling, maintain neuronal network stability, and support developmental pruning. However, when microglia are chronically primed or abnormally activated, they adopt a pro-inflammatory state characterized by heightened NF-κB signaling, increased NLRP3 levels, and heightened responses to secondary stimuli.[51] This primed state lowers the activation threshold of inflammasomes, resulting in higher levels of IL-1β and IL-18. Persistent microglial priming during critical neurodevelopmental periods can interfere with synapse formation and neural circuit growth, possibly leading to lasting behavioral and cognitive issues. Preclinical studies suggest that inflammasomes play a role in conditions linked to ASD. Animal models that use maternal immune activation and valproic acid exposure, common methods to replicate specific neurobiological aspects of ASD, show increased levels of inflammasome components in the hippocampus and striatum.[52,53] These regions are vital for social cognition, reward, and repetitive behaviors. The rise in NLRP3, ASC, and active caspase-1 suggests that inflammasome cytokine signaling may influence the formation of dysfunctional neural circuits. These findings reinforce the broader evidence that ongoing NLRP3 activation contributes to neuroinflammation in different CNS disorders, suggesting a similar mechanism may exist in ASD. Importantly, these experimental models demonstrate that inflammasome activation is associated with ASD-relevant phenotypes including impaired sociability, repetitive behaviors, and altered cognitive flexibility. Recent experimental evidence has further strengthened the causal association between NLRP3 inflammasome activation and ASD-like behavioral abnormalities. In a valproic acid-induced autism model,[3] significant upregulation of NLRP3, caspase-1, gasdermin-D, and IL-1β was observed in the hippocampus of autistic rats, accompanied by social deficits, repetitive behaviors, and neuroinflammatory changes. Importantly, pharmacological intervention with salidroside significantly attenuated NLRP3/caspase-1/gasdermin-D signaling, reduced neuroinflammation, and improved behavioral outcomes. These findings support the hypothesis that inflammasome-mediated pyroptotic pathways may contribute to ASD-related neuropathology; however, confirmation in human studies remains necessary. Such observations further support the concept that NLRP3 signaling constitutes a promising therapeutic target for immune-associated ASD phenotypes [53]. Shared mechanisms, including IL-1β-mediated synaptic dysfunction, BDNF suppression, and neuroinflammatory signaling, are discussed in Section 4. In ASD, these mechanisms are particularly relevant because they occur during critical periods of neurodevelopment and synaptic circuit formation. These inflammasome-associated synaptic abnormalities are strongly linked to behavioral manifestations of ASD, including social communication deficits, repetitive behaviors, altered sensory processing, and impaired adaptive learning. Beyond immune priming and cytokine signaling, mitochondrial dysfunction provides critical intracellular activation signals required for sustained NLRP3 inflammasome assembly in ASD. Mitochondrial dysfunction plays a crucial role in connecting ASD pathology with inflammasome activation. Many individuals with ASD show altered mitochondrial bioenergetics, increased oxidative stress markers, and impaired electron transport chain function.[43] Mitochondrial stress is a known trigger for NLRP3 activation, mainly through the production of reactive oxygen species and the release of oxidized mitochondrial

DNA into the cytosol.[3] Oxidized mitochondrial DNA can directly interact with NLRP3, encouraging its oligomerization and facilitating inflammasome assembly. In microglia, mitochondrial dysfunction leads to elevated reactive oxygen species production and impaired PTEN-induced putative kinase 1/Parkin-mediated mitophagy, resulting in the accumulation of damaged mitochondria and sustained activation of the NLRP3 inflammasome. The evidence gathered supports a mechanistic framework in which gut dysbiosis and subsequent changes in microbial metabolites drive priming of the peripheral immune system via TLR4–NF-κB signaling, while microglial mitochondrial dysfunction and oxidative stress serve as secondary signals for activation of the NLRP3 inflammasome, resulting in the release of IL-1β and IL-18, and leading to impaired synaptic plasticity, altered excitation/inhibition balance, and dysregulated neurotrophic signaling and developmental synaptic pruning. These converging neuroimmune mechanisms result in behavioral abnormalities relevant to ASD, including social deficits, repetitive behaviors, sensory dysfunction, and cognitive impairment. This integrated microbiota–microglia–inflammasome framework provides a coherent mechanistic explanation of the link between peripheral immune dysregulation and central neurodevelopmental pathology in ASD.

6. Limitations of current evidence for NOD-like receptor family pyrin domain-containing 3 involvement in autism spectrum disorder

Despite this growing interest in the role of the NLRP3 inflammasome in ASD, several important limitations warrant consideration when interpreting the available evidence. Most studies supporting the role of the inflammasome are based on animal models, including maternal immune activation and valproic acid-induced models, or on peripheral blood cytokine measurements, rather than direct investigation of human brain tissue. Therefore, the current evidence is largely associative between inflammasome-related inflammatory signaling and ASD, rather than conclusive to determine a direct causative relationship. Direct evidence of increased NLRP3 inflammasome assembly, ASC speck formation, or caspase-1 activation in the brains of ASD subjects is also sparse. Some studies have reported elevated circulating levels of IL-1β and IL-18, but these findings have not been universally replicated across ASD cohorts, highlighting the marked biological and clinical heterogeneity. Differences in age, symptom severity, co-morbidities, medication exposure, and analytical methods may account for these inconsistencies. An additional limitation is the lack of knowledge about sex- and age-dependent effects of inflammasome signaling in ASD. Due to the strong male predominance of ASD and the dynamic changes in immune function across neurodevelopmental stages, it is currently unknown whether NLRP3 activation is equally relevant across sex and developmental stages. Future studies using postmortem brain tissue, novel neuroimaging approaches, single-cell transcriptomics, and longitudinal clinical cohorts will be required to define the causal importance of NLRP3 signaling in ASD pathophysiology and to identify patient populations most likely to benefit from inflammasome-targeted interventions.

7. Mechanistic role of NOD-like receptor family pyrin domain-containing 3 in stress-related disorders

A major mechanistic question in stress-related neuropsychiatric disorders is how chronic psychological stress is transformed into persistent neuroinflammatory and behavioral abnormalities. Increasing evidence suggests that the NLRP3 inflammasome acts as a molecular interface linking neuroendocrine stress signaling, mitochondrial dysfunction, microglial activation, and stress-associated behavioral phenotypes. Chronic psychological stress significantly disrupts neuroimmune balance.[57,58] Recent studies identify the NLRP3 inflammasome as a key molecular connection between stress responses and neuroinflammation.[44,59] The stress response mainly activates the HPA axis and sympathetic nervous system. While beneficial in the short term, prolonged activation can be damaging. Continuous activation of the HPA axis keeps glucocorticoid levels elevated. Importantly, if glucocorticoid receptor signaling is disrupted, these hormones may shift from anti-inflammatory to pro-inflammatory functions. Long-term exposure to glucocorticoids may cause receptor desensitization or resistance, compromising negative feedback and leading to unchecked production of inflammatory mediators.[60] Meanwhile, sympathetic activation raises circulating catecholamines, impacting immune cell migration and cytokine release.[58] These neuroendocrine changes overall affect immune signaling pathways, leading to a heightened inflammatory response.[57] Extended stress elevates NF-κB activity in peripheral immune cells and central glial cells, enhancing the transcription of NLRP3 and pro-IL-1β.[59,61] This begins the priming stage of inflammasome activation, lowering the threshold for its assembly. Chronic stress causes microglia to develop a sensitized phenotype, characterized by increased levels of inflammasome components and a heightened response to secondary triggers such as mitochondrial dysfunction or ionic imbalances.[44] Stress-induced oxidative stress, marked by increased reactive oxygen species, supplies the necessary

activation signal for inflammasome formation.[45] Common mitochondrial disturbances in chronic stress promote the release of oxidized mitochondrial DNA and expose cardiolipin, facilitating NLRP3 oligomerization.[45,62–67] Thus, stress not only primes but also actively supports inflammasome activation. Direct mechanistic evidence of stress-induced mitochondrial dysfunction triggering NLRP3-dependent neuroinflammation has recently been demonstrated *in vivo*.[68–70] Several studies employed chronic social defeat stress paradigms to demonstrate that enhanced endoplasmic reticulum-mitochondria coupling in microglia drives mitochondrial dysfunction, inflammatory signaling, and depression-like behavioral phenotypes.[71–77] These findings provide further support that mitochondrial stress is a critical upstream trigger of NLRP3 inflammasome activation in stress-sensitive brain regions. Moreover, a growing body of evidence supports that pharmacological suppression of NLRP3 signaling significantly reduces anxiety- and depression-like behaviors in experimental stress models. For example, recent studies have demonstrated that inhibition of NLRP3 activation reduced neuroinflammatory responses, restored hippocampal function, and improved behavioral outcomes, supporting a causal role of inflammasome activation in stress-related neuropsychiatric disorders rather than being activated secondary to chronic stress exposure.[18,77]

In addition to the hippocampus's susceptibility, inflammasome activation impacts the amygdala and prefrontal cortex, which play roles in fear conditioning, threat detection, and decision-making.[59] Persistent NLRP3 activation in these regions boosts microglial activity and sustains ongoing inflammatory feedback loops.[44] IL-18, another inflammasome byproduct, can enhance T cell-mediated inflammation and boost interferon gamma levels, supporting ongoing systemic immune responses.[64,65] The connection between brain and body inflammation becomes especially important in chronic stress, where circulating cytokines can damage the blood–brain barrier and sustain microglial activation.[38,64]

Although the downstream consequences of inflammasome activation overlap with those observed in ASD, stress-related disorders are uniquely characterized by chronic HPA axis activation, glucocorticoid resistance, microglial sensitization, and impaired stress adaptation. Overall, the present data support a mechanistic model whereby chronic psychological stress results in long-lasting activation of the HPA axis and sympathetic dysregulation leading to NLRP3 inflammasome priming via an NF-κB-dependent mechanism. Concomitant mitochondrial dysfunction, oxidative stress, and ionic imbalance serve as secondary activation signals that allow inflammasome assembly in microglia. The subsequent secretion of IL-1β and IL-18 disrupts hippocampal neurogenesis, impairs synaptic plasticity, and modulates glucocorticoid receptor signaling, thereby perpetuating inflammatory feedback loops throughout stress-sensitive regions of the brain, including the hippocampus, amygdala, and prefrontal cortex. These converging neuroimmune alterations eventually give rise to persistent anxiety-, depression-, and stress-related behavioral phenotypes.

8. Therapeutic targeting of the microbiota–NOD-like receptor family pyrin domain-containing 3 axis

Therapeutic modulation of the microbiota–NLRP3 axis is an emerging translational approach that integrates innate immune therapies, microbial ecology, and metabolic regulation.[67] Given that the NLRP3 inflammasome is essential for the maturation of IL-1β and IL-18, pyroptosis signaling, and neuroinflammatory responses, direct drug targeting of NLRP3 has become a key area of research.[68] Among small-molecule inhibitors, MCC950 is the most thoroughly studied and well-understood compound. It binds to the NACHT domain of NLRP3 and inhibits its ATPase activity, preventing the conformational changes and oligomerization required for inflammasome assembly.[69,70] By selectively targeting NLRP3 rather than broadly affecting innate immune signaling, MCC950 reduces caspase-1 activation and cytokine maturation while preserving other inflammasome pathways, such as AIM2 and NLRC4.[68] Current therapeutic strategies targeting the microbiota–NLRP3 axis and their mechanisms of action are summarized in Table 2. In preclinical neuroinflammation models, pharmacological suppression of NLRP3 lowers microglial activation, reduces IL-1β release, and enhances neuronal function.[71,72] These results underscore the therapeutic potential of targeting inflammasome assembly. However, the systemic sustained suppression of NLRP3 could reduce immune defenses and hinder tissue repair, as balanced inflammasome activity can be beneficial in certain contexts.[68] Consequently, current translational research aims to develop tissue-specific delivery techniques, optimize dosing strategies, and create more effective inhibitors with improved pharmacokinetics and safety profiles.[70] Besides directly targeting inflammasomes, upstream approaches aim to restore microbial balance to modulate NLRP3 activation thresholds. Factors like reduced SCFAs, altered bile acid profiles, and disrupted tryptophan metabolism collectively increase priming and activation signals for inflammasomes.[73] Using probiotic or psychobiotic therapies to boost microbial diversity has shown promise in strengthening the epithelial

barrier, lowering systemic endotoxemia, and decreasing NF-κB-driven priming of NLRP3. Recent preclinical studies further demonstrated that probiotic-based interventions suppress NLRP3 inflammasome activation, restore BDNF signaling, and improve stress-associated behavioral abnormalities, providing translational support for microbiota-targeted approaches in neuropsychiatric disorders.[74] Certain commensal strains encourage the growth of regulatory T cells and elevate butyrate levels, providing anti-inflammatory benefits by inhibiting histone deacetylases and activating G-protein-coupled receptors.[70] These strains enhance the mucosal barrier and decrease circulating lipopolysaccharide exposure, thereby indirectly inhibiting the priming phase of inflammasome activation.[74] Supplementing with SCFAs offers a more direct metabolic strategy by restoring the immunoregulatory environment disturbed by dysbiosis. Experimental research shows that butyrate and propionate can reduce excessive IL-1β production and attenuate activation signals associated with oxidative stress, affecting both stages of inflammasome formation.[75–77] Fecal microbiota transplantation has been studied as a means to restore the overall microbial ecosystem, with early results showing improvements in gastrointestinal and behavioral symptoms in some cases of neurodevelopmental disorders.[56] Although the exact mechanisms of fecal transplantation are still being studied, its ability to influence metabolite levels and immune responses indicates it may affect inflammasome regulation.[77] An integrated translational approach increasingly recognizes that effectively modulating the

Table 2. Current therapeutic strategies targeting the microbiota–NLRP3 axis and their mechanisms in neuroinflammatory disorders

Therapeutic strategy	Representative examples	Mechanism of action	Effect on NLRP3 signaling	Level of evidence	Key references
Direct NLRP3 inhibitors	MCC950	Inhibits NACHT ATPase activity and prevents NLRP3 oligomerization	Suppresses caspase-1 activation, IL-1β maturation, and pyroptosis	Preclinical	68–70
Caspase-1 inhibitors	VX-765, Ac-YVAD-cmk	Blocks caspase-1 enzymatic activity and cytokine cleavage	Reduces IL-1β and IL-18 maturation	Preclinical/ Early clinical	17,18
Probiotics/ Psychobiotics	*Lactobacillus* spp., *Bifidobacterium* spp.	Restores microbial balance, improves epithelial barrier integrity, modulates immune signaling	Reduces NF-κB-mediated priming of NLRP3	Preclinical/ Clinical	8,74
SCFA supplementation	Butyrate, propionate	HDAC inhibition, GPR43/ GPR41 activation, Treg induction	Suppresses oxidative stress and inflammasome activation	Preclinical	26,31,35
Secondary bile acid modulation	UDCA, TUDCA, FXR/TGR5 agonists	Modulates bile acid signaling and mitochondrial homeostasis	Inhibits mitochondrial ROS-associated NLRP3 activation	Preclinical	27
Tryptophan metabolite modulation	Indole-3-propionic acid, AhR agonists	Activates AhR signaling and maintains mucosal immune tolerance	Reduces microglial inflammatory priming and cytokine release	Preclinical	36,73
Antioxidant therapy	N-acetylcysteine, Nrf2 activators	Reduces ROS generation and improves mitochondrial function	Decreases oxidative stress-dependent inflammasome activation	Preclinical	68–70
Fecal microbiota transplantation	Microbiota transfer therapy	Restores microbial diversity and metabolite homeostasis	Normalizes immune balance and inflammasome activity	Clinical/ Translational	56,77
Anti-inflammatory biologics	Anakinra, canakinumab	Neutralizes IL-1β signaling or blocks IL-1 receptor activity	Inhibits downstream inflammasome-mediated neuroinflammation	Clinical	66

Abbreviations: AhR: Aryl hydrocarbon receptor; FXR: Farnesoid X receptor; GPR: G protein-coupled receptor; HDAC: Histone deacetylase; IL: Interleukin; NACHT: NAIP, CIITA, HET-E, and TP1 domain; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like receptor family pyrin domain-containing 3; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; TGR5: Takeda G protein-coupled receptor 5; Treg: Regulatory T cell; TUDCA: Tauroursodeoxycholic acid; UDCA: Ursodeoxycholic acid.

microbiota–NLRP3 axis will likely require precise patient stratification rather than a universal solution. Progress in metagenomic sequencing, metabolomics, and immune phenotyping now enables the identification of microbial signatures and inflammatory biomarkers linked to increased inflammasome activity.[67] Recent advances in translational inflammasome research have accelerated the development of biomarker-guided therapeutic strategies targeting NLRP3 signaling. Emerging evidence supports the use of circulating IL-1β, IL-18, ASC specks, caspase-1 activity, and inflammasome-associated metabolic signatures as clinically relevant markers of pathway activation and treatment responsiveness. Moreover, growing knowledge of the molecular mechanisms regulating NLRP3 assembly has propelled the development of next-generation inflammasome inhibitors with improved selectivity and therapeutic potential. Recent reviews have highlighted the growing clinical interest in NLRP3-targeted interventions for neuroinflammatory, neurodegenerative, and immune-mediated disorders, underscoring the need to incorporate molecular biomarkers, microbiome profiling, and precision medicine approaches to optimize patient selection and therapeutic efficacy. Such advances support the future translation of microbiota–inflammasome-based interventions into personalized treatment strategies for neurodevelopmental and stress-related disorders.[67,68,70] For instance, individuals exhibiting high circulating IL-1β levels, elevated mitochondrial stress markers, or specific dysbiotic patterns might belong to distinct biological groups that respond better to targeted NLRP3 inhibitors or microbiota-based therapies. As a result, treatment plans are increasingly personalized, combining molecular profiling with pharmacological and microbiota-focused approaches. These strategies aim to reduce overall inflammation and reestablish balance within the compromised immune-metabolic network along the gut–brain axis. The link between the microbiota and the immune system suggests that combining therapies could yield synergistic benefits. Directly inhibiting NLRP3 can decrease acute neuroinflammation, while restoring microbiota helps correct the ecological imbalances that generate priming signals. This combined approach reflects a systems-level view of neuroimmune disorders, recognizing that ongoing inflammation results from both peripheral microbial disturbances and internal cell stress responses. As knowledge about inflammasome structure, mitochondrial signaling, and microbial metabolites grows, translational research will focus more on balancing immune suppression with ecological restoration. The aim is not to completely silence the inflammasome but to restore normal physiological responses within a balanced gut–immune–brain system. This rebalancing may provide a promising treatment for neurodevelopmental and stress-related disorders marked by ongoing NLRP3 hyperactivity.

9. Limitations and controversies

There is a growing body of evidence suggesting a role for NLRP3 inflammasome signaling in microbiota-driven neuroinflammation, but several important limitations and outstanding questions remain that must be addressed to correctly interpret existing findings and successfully translate inflammasome-targeted therapies into clinical practice. A major limitation of the current literature is that much of the evidence linking NLRP3 activation to ASD and stress-related disorders is derived from animal models, *in vitro* studies, or peripheral blood biomarkers. Although elevated levels of IL-1β, IL-18, and other inflammatory mediators have been reported in several studies, direct demonstration of NLRP3 inflammasome assembly, ASC speck formation, or caspase-1 activation in human brain tissue remains limited. As a result, many proposed mechanisms are based on indirect evidence and require validation in postmortem studies, advanced neuroimaging investigations, and single-cell molecular analyses of the human brain tissue. The NLRP3 inflammasome plays an important physiological role in host defense against pathogens and in tissue repair processes. Thus, prolonged pharmacological inhibition of NLRP3 may have unintended consequences. MCC950, one of the most extensively studied NLRP3 inhibitors, has shown robust anti-inflammatory effects in preclinical models; however, the long-term safety of chronic NLRP3 suppression remains unclear. Potential concerns include impaired immune surveillance, increased susceptibility to infections, altered responses to tissue injury, and disruption of normal inflammatory homeostasis. Future clinical studies should carefully evaluate the balance between therapeutic efficacy and immune safety. Microbiota-directed interventions, including probiotics, prebiotics, postbiotics, dietary modifications, and fecal microbiota transplantation, are promising approaches for modulating inflammasome activity. However, there is substantial inter-individual variability in baseline microbial composition, dietary habits, genetic background, environmental exposures, and disease phenotypes. These factors highlight the importance of personalized, microbiome-targeted therapeutics and biomarker-guided patient stratification. Sex-dependent differences represent another important but under-explored aspect of NLRP3 biology. ASD is significantly more prevalent in males, whereas a number of stress-related disorders show sex-specific differences in prevalence, symptom presentation, and disease course. Sex hormones modulate immune responses, microglial activation, mitochondrial function, and inflammatory

signaling pathways, all of which could influence inflammasome activity. However, most preclinical studies of NLRP3 signaling have been conducted only in male animals, limiting our understanding of sex-specific mechanisms. Future studies should systematically examine the influence of biological sex on microbiota composition, inflammasome activation, and therapeutic response. Together, these limitations underscore the need for carefully designed translational studies that integrate microbiome profiling, molecular biomarkers, sex-specific analyses, and direct human evidence. The clinical relevance of NLRP3 signaling can only be established, and safe and effective microbiota-inflammasome-based therapeutic interventions can only be developed once these challenges have been addressed.

10. Conclusion

NOD-like receptor family pyrin domain-containing 3 inflammasome has emerged as an important molecular link between gut microbial dysbiosis, peripheral immune activation, and CNS pathology. Alterations in microbial composition, intestinal barrier dysfunction, and inflammatory signaling all contribute to sustained inflammasome priming, providing a mechanistic framework for how peripheral immune disturbances can affect brain function. In both ASD and stress-related disorders, chronic inflammatory priming together with mitochondrial dysfunction, oxidative stress, and impaired cellular homeostasis may promote excessive NLRP3 activation. Subsequent production of IL-1β and IL-18 contributes to neuroinflammation, impaired synaptic plasticity, altered neurotrophic signaling, and dysregulation of HPA axis feedback, thereby influencing behavioral and cognitive outcomes. Current evidence suggests that therapeutic strategies targeting both the gut microbiota and the NLRP3 signaling pathway may have greater translational potential than inflammasome suppression alone. Future studies should emphasize stratification of patients by biomarkers, direct validation in human studies, and precision medicine approaches to optimize the safety and efficacy of microbiota–inflammasome-based interventions in neurodevelopmental and stress-related pathologies.

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Further disclosure

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