Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(3): 25970
https://doi.org/10.31083/FBL25970

Review

Ubiquitin Ligases in Control: Regulating NLRP3 Inflammasome Activation

Swarna Beesetti[1,*]

[1]Department of Immunology, St Jude Children's Research Hospital, Memphis, TN 38105, USA
*Correspondence: Swarna.beesetti@stjude.org (Swarna Beesetti)

Academic Editor: Eun Sook Hwang
Submitted: 2 August 2024 Revised: 4 September 2024 Accepted: 11 September 2024 Published: 19 March 2025

Abstract

Ubiquitin ligases play pivotal roles in the regulation of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, a critical process in innate immunity and inflammatory responses. This review explores the intricate mechanisms by which various E3 ubiquitin ligases exert both positive and negative influences on NLRP3 inflammasome activity through diverse post-translational modifications. Negative regulation of NLRP3 inflammasome assembly is mediated by several E3 ligases, including F-box and leucine-rich repeat protein 2 (FBXL2), tripartite motif-containing protein 31 (TRIM31), and Casitas B-lineage lymphoma b (Cbl-b), which induce K48-linked ubiquitination of NLRP3, targeting it for proteasomal degradation. Membrane-associated RING-CH 7 (MARCH7) similarly promotes K48-linked ubiquitination leading to autophagic degradation, while RING finger protein (RNF125) induces K63-linked ubiquitination to modulate NLRP3 function. Ariadne homolog 2 (ARIH2) targets the nucleotide-binding domain (NBD) domain of NLRP3, inhibiting its activation, and tripartite motif-containing protein (TRIM65) employs dual K48 and K63-linked ubiquitination to suppress inflammasome assembly. Conversely, Pellino2 exemplifies a positive regulator, promoting NLRP3 inflammasome activation through K63-linked ubiquitination. Additionally, ubiquitin ligases influence other components critical for inflammasome function. TNF receptor-associated factor 3 (TRAF3) mediates K63 polyubiquitination of apoptosis-associated speck-like protein containing a CARD (ASC), facilitating its degradation, while E3 ligases regulate caspase-1 activation and DEAH-box helicase 33 (DHX33)-NLRP3 complex formation through specific ubiquitination events. Beyond direct inflammasome regulation, ubiquitin ligases impact broader innate immune signaling pathways, modulating pattern-recognition receptor responses and dendritic cell maturation. Furthermore, they intricately control NOD1/NOD2 signaling through K63-linked polyubiquitination of receptor-interacting protein 2 (RIP2), crucial for nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) activation. Furthermore, we explore how various pathogens, including bacteria, viruses, and parasites, have evolved sophisticated strategies to hijack the host ubiquitination machinery, manipulating NLRP3 inflammasome activation to evade immune responses. This comprehensive analysis provides insights into the molecular mechanisms underlying inflammasome regulation and their implications for inflammatory diseases, offering potential avenues for therapeutic interventions targeting the NLRP3 inflammasome. In conclusion, ubiquitin ligases emerge as key regulators of NLRP3 inflammasome activation, exhibiting a complex array of functions that finely tune immune responses. Understanding these regulatory mechanisms not only sheds light on fundamental aspects of inflammation but also offers potential therapeutic avenues for inflammatory disorders and infectious diseases.

Keywords: ubiquitin ligases; NLRP3 inflammasome; innate immunity; inflammation; post-translational modifications

1. Introduction

Inflammasomes are sophisticated multiprotein complexes that play a crucial role in innate immunity, acting as critical sensors and integrators of danger signals [1–3]. These complexes are essential for the body's initial defense against both pathogenic microorganisms pathogen-associated molecular patterns (PAMPs) and sterile incursions damage-associated molecular patterns (DAMPs) such as trauma, cancer, ischemia, and metabolic perturbations [4,5]. Typically, an inflammasome consists of three main components: a sensor protein (e.g., NOD-like receptors (NLR) family members or Pyrin and HIN domain-containing (PYHIN) proteins), an adaptor protein (usually ASC - apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD), and an effector protein (typically pro-caspase-1) [6–8].

Inflammasome activation is a tightly regulated process involving two distinct steps. The initial step, known as priming, involves the upregulation of inflammasome components and pro-forms of inflammatory cytokines, typically through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [9–12]. The second step triggers the assembly of the inflammasome complex, leading to the activation of caspase-1, which then processes inactive precursors of the cytokines interleukin-1β (IL-1β) and interleukin-18 (pro-IL-1β and pro-IL-18) into their mature, bioactive forms [9,12,13].

Several types of inflammasomes have been identified, each responding to specific stimuli and playing distinct roles in immune responses [14–17]. The NLR family pyrin domain containing 3 (NLRP3) inflammasome, for instance, is activated by a diverse range of stimuli including ATP,

pore-forming toxins, crystalline substances, and cellular stress signals, and is involved in responses to a wide array of pathogens and sterile inflammatory conditions [18]. The NLR family pyrin domain containing 1 (NLRP1) inflammasome, activated by Bacillus anthracis lethal toxin and muramyl dipeptide, plays a significant role in anthrax infection and certain autoimmune disorders [6,19]. The NLR family caspase activation and recruitment domain (CARD) domain-containing protein (NLRC4) inflammasome, often in conjunction with Neuronal Apoptosis Inhibitory Protein (NAIP) proteins, detects bacterial flagellin and components of type III secretion systems, making it critical for responding to intracellular bacterial pathogens [20,21]. The absent in melanoma 2 (AIM2) inflammasome responds to cytosolic double-stranded DNA, playing an important role in host defense against DNA viruses and intracellular bacteria [22,23]. Additionally, the Pyrin inflammasome, activated by bacterial toxins that modify Ras homolog gene family member A (RhoA) GTPases, is involved in autoinflammatory diseases and responses to certain bacterial infections [24,25].

Other inflammasomes, including Interferon-Inducible Protein 16 (IFI16), NLRP6, and NLRP7, have unique activators and roles in immune responses [17,26–28]. The activation of inflammasomes results in the proteolytic activation of inflammatory caspases, leading to the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18 [29]. Inflammasome activation can also trigger pyroptosis, a form of inflammatory cell death characterized by cellular swelling, membrane rupture, and the release of intracellular contents [30,31].

While inflammasome activation is critical for host defense, it requires tight regulation to prevent excessive inflammation and tissue damage [32,33]. Dysregulation of inflammasome activity has been associated with various inflammatory disorders, including autoinflammatory diseases, cardiometabolic diseases, infections, cancer, and neurological disorders [34,35]. In the context of intracerebral hemorrhage (ICH), edaravone has emerged as a promising neuroprotective agent due to its multifaceted mechanisms of action [36–38]. As a potent free radical scavenger, neutralizes reactive oxygen species generated from hemoglobin breakdown, potentially mitigating oxidative stress-induced neuronal damage [39]. Additionally, edaravone exhibits anti-inflammatory properties by suppressing microglial activation and reducing pro-inflammatory cytokine production [40]. Preclinical study demonstrated edaravone's ability to preserve blood-brain barrier integrity, inhibit neuronal apoptosis in the perihematomal region, and attenuate early brain injury following ICH. In animal models, edaravone treatment has been associated with reduced brain edema, decreased neurological deficits, and improved long-term functional outcomes [41]. While clinical evidence remains limited, a small randomized controlled trial showed promising results, with early edaravone administration linked to reduced hematoma growth and improved functional outcomes in ICH patients [38,42]. The diversity of inflammasome types allows for a nuanced and targeted immune response to a wide range of potential threats [43]. Understanding the specific activation mechanisms and regulatory pathways of each inflammasome type is crucial for developing targeted therapeutic strategies for various inflammatory and infectious diseases [44]. Ongoing research continues to unravel the complex interplay between different inflammasomes and their roles in health and disease.

2. NLRP3 Inflammasome Activation

The NLRP3 inflammasome is a cornerstone of the innate immune system, serving as a sophisticated sentinel that detects a wide array of pathogenic threats and cellular stresses [10]. This multiprotein complex, comprising the NLRP3 sensor protein, the ASC adaptor, and pro-caspase 1, orchestrates the initiation and amplification of inflammatory responses crucial for host defense [45].

The NLRP3 protein itself is an architectural marvel, featuring three distinct domains: a C-terminal leucine-rich repeat (LRR) domain involved in ligand sensing, a central NACHT domain that facilitates oligomerization, and an N-terminal pyrin (PYD) domain responsible for protein-protein interactions during inflammasome assembly [46]. This intricate structure allows NLRP3 to function as a molecular switch, transitioning from an inactive to an active state in response to cellular danger signals [47].

Activation of the NLRP3 inflammasome is a meticulously regulated process that typically unfolds in two stages: priming and activation. The priming phase, initiated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), activates NF-κB signaling through various pattern recognition receptors such as Toll-like receptors (TLRs), NOD2, IL-1R, or tumor necrosis factor receptor (TNFR) [45,48,49]. This signaling cascade leads to the transcriptional upregulation of NLRP3 itself, as well as its substrate pro-inflammatory cytokines, pro-IL-1β and pro-IL-18 [50–53]. Beyond transcriptional effects, priming also induces critical post-translational modifications of NLRP3, including ubiquitination and phosphorylation, which fine-tune its activation potential [54].

The activation phase, triggered by a remarkably diverse array of stimuli ranging from extracellular ATP and pore-forming toxins to particulate matter and various pathogens, initiates the assembly of the inflammasome complex [1]. While the precise mechanism by which NLRP3 recognizes such a broad spectrum of activators remains a subject of intense research, emerging evidence suggests that NLRP3 likely senses common cellular perturbations induced by these stimuli rather than directly binding to them [55]. One proposed mechanism involves the disassembly of the trans-Golgi network (TGN), which serves as a cellular stress indicator that can recruit and activate NLRP3 [47,56].

Upon activation, NIMA-related kinase 7 (NEK7) emerges as a critical player, binding to NLRP3 and inducing a conformational change that disrupts its inactive double-ring structure [57]. This structural rearrangement exposes the PYD domains, allowing the NACHT domain to oligomerize [58]. The exposed PYD domain then recruits the adaptor molecule ASC, forming a remarkable filamentous structure known as the ASC pyroptosome or "speck" [59]. This speck serves as a molecular platform, with the caspase recruitment domain (CARD) of ASC binding to pro-caspase-1 and facilitating its conversion to active caspase-1 through proximity-induced autoproteolysis [60,61].

Activated caspase-1 functions as the effector arm of the inflammasome, processing the pro-forms of IL-1β and IL-18 into their bioactive states [62]. Additionally, caspase-1 cleaves gasdermin D (GSDMD), a key mediator of pyroptosis, a highly inflammatory form of programmed cell death [63]. The N-terminal domain of cleaved GSDMD oligomerizes to form pores in the cell membrane, leading to cellular swelling, lysis, and the release of intracellular contents, including the mature inflammatory cytokines IL-1β and IL-18 [64].

The NLRP3 inflammasome is tightly regulated through multiple mechanisms to maintain immune homeostasis. Autophagy plays a crucial role in limiting NLRP3 activation by promoting its degradation [65]. MicroRNAs, particularly miR-223, negatively regulate NLRP3 expression by targeting its mRNA [50,65]. Anti-inflammatory cytokines like IL-10 suppress NLRP3 activity [45], while endogenous inhibitors such as CARD8 and pyrin-only proteins provide additional control [66,67]. Species-specific differences in NLRP3 activation exist between humans and mice, highlighting the importance of careful interpretation in translational research [68]. Recent structural biology insights have revealed conformational changes during NLRP3 activation, enhancing our understanding of its molecular mechanisms [67]. Cellular metabolism, especially glycolysis and mitochondrial function, significantly influences NLRP3 activation [47]. NLRP3 function varies across different tissue contexts, with distinct roles in immune cells versus epithelial cells [69]. From an evolutionary perspective, NLRP3 is conserved across species, suggesting its fundamental importance in innate immunity [70].

Complementing this canonical pathway, NLRP3 inflammasome activation can also proceed through a non-canonical route mediated by caspase-4 and caspase-5 in humans, or caspase-11 in mice [71,72]. This pathway is particularly relevant in the context of intracellular LPS detection from Gram-negative bacteria, further expanding the surveillance capacity of the inflammasome system [50,73].

The exquisite regulation of NLRP3 inflammasome activation is paramount for maintaining immune homeostasis [66]. Dysregulation of this process has been implicated in a spectrum of inflammatory disorders, ranging from autoinflammatory diseases to metabolic syndromes and neurodegenerative conditions [74]. This central role in health and disease has positioned the NLRP3 inflammasome as a prime target for therapeutic interventions, with ongoing research exploring various strategies to modulate its activity in inflammatory diseases [75].

3. Post Translational Modifications of NLRP3

Post-translational modifications (PTMs) play a pivotal role in regulating the activity of the NLRP3 inflammasome, a critical component of innate immunity responsible for detecting cellular stress and pathogen invasion [76,77]. These PTMs exert precise control over NLRP3 function, influencing its activation, assembly into the inflammasome complex, and subsequent cytokine secretion [56,78].

Phosphorylation plays a critical and multifaceted role in regulating NLRP3 inflammasome activation, with different phosphorylation sites exerting diverse and sometimes opposing effects [79]. At Ser295 (human)/Ser293 (mouse), phosphorylation by protein kinase D (PKD) at the Golgi apparatus promotes activation. In contrast, phosphorylation by protein kinase A (PKA) inhibits activation by suppressing the ATPase activity of the NLRP3 NACHT domain. At Ser5 (human)/Ser3 (mouse), phosphorylation by AKT has a dual role: it impedes inflammasome activation by inhibiting NLRP3 oligomerization and prevents proteasome-mediated degradation of NLRP3 during lipopolysaccharide (LPS) priming. Dephosphorylation of this site by protein phosphatase 2A (PP2A) enhances activation by promoting NLRP3-ASC interaction [45,80,81]. Additionally, phosphorylation at Ser198 (human)/Ser194 (mouse) by c-Jun N-terminal kinase 1 (JNK1) facilitates NLRP3 homo-oligomerization and is essential for inflammasome activation [82]. In contrast, enhanced tyrosine phosphorylation at Tyr861 negatively regulates inflammasome activation through autophagy induction, with protein tyrosine phosphatase nonreceptor 22 (PTPN22) promoting activation by dephosphorylating this site [77,83].

Ubiquitination plays a crucial role in regulating NLRP3 inflammasome function through various linkage types, with the balance between ubiquitination and deubiquitination being essential for controlling inflammasome activation [84]. K48-linked ubiquitination targets NLRP3 for proteasomal degradation, inhibiting inflammasome activation [85]. Several E3 ubiquitin ligases mediate this process, including TRIM31, which promotes K48-linked polyubiquitination of NLRP3 [45]. Other E3 ligases such as MARCH7, ARIH2, and FBXL2 also attenuate NLRP3 inflammasome activation through protein degradation [86]. K63-linked ubiquitination, present in resting macrophages, has been associated with NLRP3 regulation. The E3 ubiquitin ligase TRIM65 can induce both K48- and K63-linked ubiquitination of NLRP3, with a higher efficiency for K63-linked ubiquitination. Deubiquitination enhances inflammasome activation, with BRCA1/BRCA2-containing com-

plex 3 (BRCC3), a component of the BRCC36 isopeptidase complex (BRISC), acting as a positive regulator by promoting deubiquitination of the Leucine Rich Repeat (LRR) region of NLRP3 [86]. The USP1-Associated Factor 1/Ubiquitin-Specific Peptidase 1 UAF1/USP1 deubiquitinase complex specifically removes K48-linked ubiquitination of NLRP3, stabilizing its expression and facilitating inflammasome activation [84].

Other post-translational modifications (PTMs) intricately regulate NLRP3 inflammasome activity through diverse mechanisms. SUMOylation, mediated by the E3 ligase MAPL (MUL1), inhibits NLRP3 by preventing its oligomerization and interaction with ASC, thereby blocking inflammasome assembly and activation [45,87,88]. S-nitrosylation at cysteine residues, such as Cys3 and Cys394, by nitric oxide (NO) donors, impedes NLRP3 oligomerization and inflammasome formation [89]. ADP-ribosylation mediated by Poly (ADP-ribose) polymerase 1 (PARP1) suppresses NLRP3 activation by disrupting its interaction with NIMA-related kinase 7 (NEK7), which is crucial for inflammasome assembly [90]. Acetylation at lysine residues by p300/CBP enhances NLRP3 activation, promoting its interaction with ASC and facilitating IL-1β secretion [91]. O-GlcNAcylation at Ser198 inhibits NLRP3 inflammasome activation by disrupting its association with ASC and caspase-1, thus reducing IL-1β production [66]. Nitration of Tyr861 by reactive nitrogen species (RNS) attenuates NLRP3 activation, lowering IL-1β secretion and inflammation [89]. Glycosylation at Asn451 stabilizes NLRP3, enhancing inflammasome activity, while methylation of specific residues can alter NLRP3's interaction dynamics and affect its assembly and activation [13]. Palmitoylation of cysteine residues regulates NLRP3 membrane association, potentially modulating its activation state and influencing inflammasome function [92]. These PTMs collectively orchestrate the precise regulation of NLRP3 inflammasome responses to various stimuli, crucial for maintaining immune homeostasis and responding appropriately to pathogens and cellular stress.

4. Roles of Key Ubiquitin Ligases in NLRP3 Inflammasome Regulation

The intricate regulation of the NLRP3 inflammasome is heavily influenced by various post-translational modifications (PTMs), with ubiquitination playing a pivotal role [93]. Understanding these modifications is crucial for developing targeted therapies to modulate inflammasome activity in inflammatory and immune-related diseases [78]. Ubiquitin ligases, through the addition of ubiquitin molecules, exert precise control over NLRP3's stability, localization, and activity, ultimately modulating inflammasome activation [94]. These modifications can either tag NLRP3 for degradation or facilitate its assembly and activation, thus balancing the immune response to prevent both insufficient and excessive inflammation [56]. Understanding the specific ubiquitin ligases involved in these processes is crucial for comprehending the broader regulatory mechanisms at play. Each ubiquitin ligase, including TRIM31, MARCH7, FBXL2, Pellino2, and TRAF6, contributes uniquely to the modulation of NLRP3 activity through distinct ubiquitination pathways [1,77]. Below, we delve into the detailed roles of these key ubiquitin ligases and their impact on NLRP3 inflammasome regulation (Fig. 1) created using Biorender (https://biorender.com/).

5. Negative Regulators of NLRP3 Inflammasome

Understanding the negative regulation of the NLRP3 inflammasome is crucial for comprehending how the body maintains immune homeostasis and prevents excessive inflammation. Several ubiquitin ligases act as key negative regulators, mediating the ubiquitination and subsequent proteasomal degradation of NLRP3, thus limiting its activation. These ubiquitin ligases ensure that the NLRP3 inflammasome is tightly controlled, preventing unwarranted inflammatory responses that can lead to chronic inflammation and autoimmune diseases [94].

5.1 TRIM31

TRIM31, a member of the TRIM protein family with E3 ubiquitin ligase activity, intricately regulates NLRP3 inflammasome activation through multifaceted mechanisms [95]. It directly binds to NLRP3 via its PYD domain, facilitating both K48-linked ubiquitination for proteasomal degradation and K63-linked ubiquitination that enhances NLRP3 oligomerization and assembly with ASC, thereby promoting inflammasome activation [85]. This dual regulatory role of TRIM31 is pivotal in modulating immune responses: it negatively regulates NLRP3 by promoting degradation to prevent hyperinflammation, while positively influencing inflammatory responses through assembly promotion. Experimental evidence demonstrates that TRIM31 overexpression decreases NLRP3 levels and IL-1β production, whereas its deficiency increases inflammasome activation, exacerbating inflammatory conditions such as DSS-induced colitis [85]. These findings underscore TRIM31's complex role in fine-tuning NLRP3 inflammasome activity, suggesting potential therapeutic avenues for modulating inflammation in various diseases.

5.2 MARCH7

Membrane-Associated Ring-CH-Type Finger 7 (MARCH7) is a member of the MARCH family of E3 ubiquitin ligases, characterized by the presence of a Really Interesting New Gene-Cysteine/Histidine-rich (RING-CH) domain essential for their ubiquitin ligase activity [96]. MARCH7 specifically targets the NLRP3 protein for ubiquitination, catalyzing the addition of K48-linked polyubiquitin chains to NLRP3, typically signaling it for degradation [97]. Unlike other E3 ligases that promote proteasomal degradation, MARCH7 mediates the autophagic degradation of NLRP3 [98]. This distinct autophagic path-

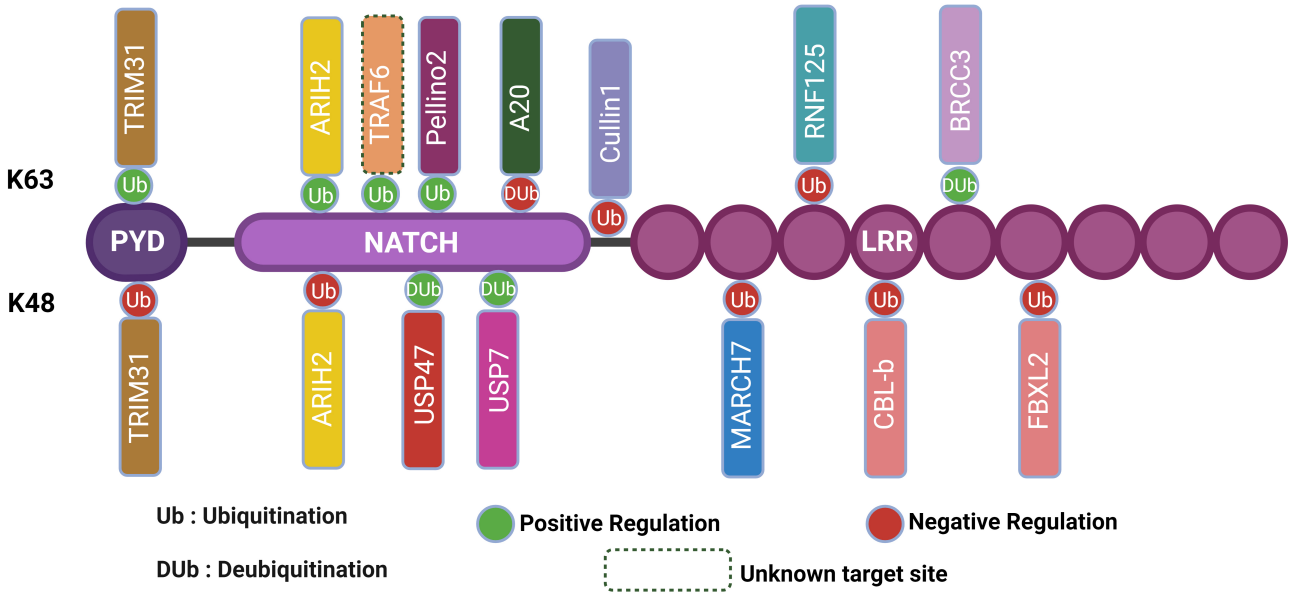

Fig. 1. Regulation of NLRP3 inflammasome activation through ubiquitination and deubiquitination mechanisms. The figure illustrates the regulation of the NLRP3 inflammasome through ubiquitination and deubiquitination mechanisms. The NLRP3 inflammasome consists of the (Pyrin Domain) PYD, Nucleotide-binding domain, NATCH, and Leucine-Rich Repeat (LRR) domains. Positive regulation occurs via K63 ubiquitination by TRIM31 and ARIH2, promoting inflammasome activation, while negative regulation is mediated by K48 ubiquitination by the same proteins, leading to inhibition. Deubiquitinating enzymes such as USP47, USP7, and BRCC3 remove ubiquitin, thereby influencing inflammasome activity. Additionally, other regulatory proteins, including TRAF6, Pellino2, A20, Cullin1, RNF125, MARCH7, CBL-b, and FBXL2, modulate inflammasome activity through various ubiquitination pathways. The legend indicates ubiquitination (Ub), deubiquitination (DUb), positive regulation (green circles), negative regulation (red circles), and unknown target sites (dashed lines). This figure highlights the complex interplay of post-translational modifications in regulating NLRP3 inflammasome activation. Created using BioRender.com. NLRP3, NLR family pyrin domain containing 3; BRCC3, BRCA1/BRCA2-containing complex subunit 3; TRIM31, Tripartite Motif Containing 31; ARIH2, Ariadne RBR E3 Ubiquitin Protein Ligase 2; TRAF6, TNF Receptor-Associated Factor 6; RNF125, Ring Finger Protein 125; MARCH7, Membrane-Associated Ring-CH-Type Finger 7; CBL-b, Casitas B-Lineage Lymphoma-b; FBXL2, F-Box And Leucine Rich Repeat Protein 2.

way helps regulate NLRP3 levels and activity. MARCH7 binds to the Leucine-Rich Repeat (LRR) and NACHT domains of NLRP3, which are critical for its function in inflammasome formation. This specific interaction does not affect other inflammasome components such as ASC or Pro-Caspase-1, highlighting MARCH7's targeted regulation [66].

By promoting the degradation of NLRP3, MARCH7 acts as a negative regulator, suppressing the formation and activation of the NLRP3 inflammasome [66]. This process reduces NLRP3 protein levels, preventing unnecessary or excessive inflammasome activation and maintaining cellular homeostasis under basal conditions. This process is intricately linked to the dopamine D1 receptor pathway, providing a fascinating connection between neurotransmitter signaling and innate immunity [50]. By promoting NLRP3 degradation in response to dopaminergic stimulation, MARCH7 contributes to the anti-inflammatory effects of dopamine, effectively inhibiting NLRP3 inflammasome activation. This dopamine-MARCH7-NLRP3 axis represents a sophisticated regulatory mechanism that highlights the intricate crosstalk between the nervous system and inflammatory processes [99]. A Study showed that overexpression of MARCH7 decreases NLRP3 protein levels and IL-1β production, while its knockdown results in increased NLRP3 levels and enhanced inflammasome activation [98]. Enhancing MARCH7 activity or expression could be a strategy for dampening excessive NLRP3-mediated inflammation, beneficial in treating diseases like gout, atherosclerosis, and certain autoimmune conditions. Understanding MARCH7's interplay with other NLRP3 regulators, such as TRIM31 and FBXL2, and further research into the dopamine-MARCH7-NLRP3 axis, could provide new therapeutic approaches for managing NLRP3-associated inflammatory disorders.

5.3 RNF125

Ring Finger Protein 125 (RNF125) is an E3 ubiquitin ligase that plays a crucial role in the regulation of the NLRP3 inflammasome. RNF125 initiates K63-linked polyubiquitination of the NLRP3 leucine-rich repeat (LRR) domain, a modification that facilitates the recruitment of an-

other E3 ubiquitin ligase, Cbl-b [100]. By targeting NLRP3 for K63-linked ubiquitination, RNF125 sets the stage for a two-step process that ultimately controls NLRP3 protein levels and inflammasome activity [100]. This mechanism creates a negative feedback loop to control inflammation, particularly in the context of viral infections where type I interferons are prominently induced. By reducing NLRP3 protein levels, RNF125 suppresses inflammasome assembly and activation, leading to decreased production of pro-inflammatory cytokines like IL-1β and IL-18 [100]. This function is particularly important in preventing excessive or prolonged NLRP3 inflammasome activation, helping to maintain immune homeostasis [77].

5.4 CBL-b

Casitas B-lineage Lymphoma-b (Cbl-b) is another E3 ubiquitin ligase involved in the regulation of the NLRP3 inflammasome [100]. Cbl-b specifically targets the LRR domain of NLRP3 for K48-linked polyubiquitination, also leading to proteasomal degradation. By targeting NLRP3 for degradation, Cbl-b acts as a negative regulator, preventing the excessive activation of the inflammasome [100]. This regulation is critical for balancing immune responses and avoiding hyperinflammation. Research indicates that Cbl-b deficiency leads to increased NLRP3 levels and heightened inflammasome activity, contributing to exacerbated inflammatory conditions [45]. The role of Cbl-b in inflammasome regulation underscores the importance of ubiquitin-mediated pathways in controlling innate immune responses. Furthermore, the negative regulation of NLRP3 inflammasome activation by Cbl has been associated with the inhibition of glycolysis through GLUT1-dependent mechanisms [101]. By inhibiting Cbl, there is an increase in GLUT1 expression, leading to enhanced glycolytic capacity and subsequent NLRP3 inflammasome activation [101]. This demonstrates the diverse pathways through which proteins like Cbl modulate NLRP3 activity.

5.5 FBXL2

F-box and Leucine-rich repeat protein 2 (FBXL2) is a critical regulator of the NLRP3 inflammasome, functioning as part of the Skp1-Cullin-F-box (SCF) E3 ubiquitin ligase complex [102]. This complex consists of Skp1, Cullin1, Rbx1, and FBXL2 as the F-box protein that determines substrate specificity. FBXL2 directly interacts with NLRP3 through its leucine-rich repeats (LRRs), specifically targeting Lysine689 of NLRP3 for ubiquitination [77,103]. It facilitates the addition of K48-linked polyubiquitin chains to NLRP3, marking it for proteasomal degradation by the 26S proteasome [104]. This process effectively reduces cellular levels of NLRP3, thereby inhibiting inflammasome activation and decreasing production of pro-inflammatory cytokines like IL-1β and IL-18 [104].

FBXL2's activity is modulated by various cellular signals, including JNK1-mediated phosphorylation, which enhances its ability to target NLRP3 [10]. Interestingly, FBXL2 itself is regulated by another F-box protein, FBXO3, creating a regulatory loop where TLR signaling can indirectly increase NLRP3 levels by reducing FBXL2-mediated degradation [105]. This mechanism helps maintain homeostasis under basal conditions and plays a crucial role in resolving inflammation after the initial immune response.

Experimental evidence underscores FBXL2's importance, showing that its overexpression decreases NLRP3 levels and reduces inflammasome activation, while its knockdown has the opposite effect [103]. Dysregulation of FBXL2 could potentially contribute to excessive NLRP3 activation in various inflammatory disorders, making it a promising therapeutic target [45].

5.6 ARIH2

Ariadne RBR E3 Ubiquitin Protein Ligase 2 (ARIH2), a member of the Ring-Between-Ring (RBR) family of E3 ubiquitin ligases, plays a pivotal role in modulating NLRP3 inflammasome activation through its distinctive ubiquitin ligase activity [106,107]. It specifically targets NLRP3 for ubiquitination, catalyzing both K48-linked and K63-linked polyubiquitination. While K48-linked ubiquitination typically marks proteins for proteasomal degradation, the exact consequences of ARIH2-mediated ubiquitination on NLRP3 function are still under investigation [108]. This dual mode of ubiquitination by ARIH2 highlights its nuanced regulatory role in fine-tuning inflammasome activity, potentially impacting the formation and activation of the NLRP3 complex [109]. This mechanism is crucial during the priming phase of NLRP3 activation, influencing the expression and assembly of inflammasome components in response to inflammatory cues.

ARIH2's interaction with NLRP3 is pivotal in macrophages, where it negatively regulates inflammasome activation. By modifying NLRP3 through ubiquitination, ARIH2 likely modulates its stability or activity, thereby affecting downstream inflammatory responses mediated by IL-1β and IL-18 [50]. ARIH2 as a potential therapeutic target in inflammatory diseases characterized by NLRP3 hyperactivation.

5.7 Cullin1

Cullin1, as an essential component of the Skp1-Cullin1-F-box (SCF) E3 ubiquitin ligase complex, plays a critical role in regulating NLRP3 inflammasome activation through its distinct mechanism. Structurally, Cullin1 acts as a scaffold within the SCF complex, facilitating the assembly of Skp1, an F-box protein, and a RING protein (typically Rbx1). This complex formation is crucial for its function as an E3 ubiquitin ligase. Interaction studies have revealed that Cullin1 directly interacts with the PYD domain of NLRP3 [45,110]. This interaction facilitates the specific ubiquitination of NLRP3, particularly through K63-linked polyubiquitin chains [111]. Unlike K48-linked ubiquitination, which typically targets proteins for proteasomal degra-

dation, K63-linked ubiquitination serves primarily as a signaling mechanism involved in protein-protein interactions and cellular signaling pathways.

Specifically, Cullin1 promotes K63-linked ubiquitination at lysine 689 (K689) of NLRP3. This modification plays a pivotal role in preventing NLRP3 inflammasome assembly and activation under basal conditions [112]. By ubiquitinating NLRP3 in this manner, Cullin1 interferes with the assembly of the NLRP3 inflammasome complex or its responsiveness to activating signals, thereby maintaining NLRP3 in an inactive state [13]. This regulatory role of Cullin1 is distinct from other E3 ligases such as TRIM31 or FBXL2, which primarily induce proteasomal degradation of NLRP3 [105]. The non-degradative nature of K63-linked ubiquitination by Cullin1 suggests a mechanism for finely tuning NLRP3 activity without the need for protein degradation, enabling rapid activation or inactivation as needed by the cell [77]. Understanding the intricate regulatory mechanisms involving Cullin1 and NLRP3 provides insights into how cells tightly control inflammatory responses. This knowledge could potentially lead to new therapeutic strategies for managing NLRP3-associated inflammatory disorders by modulating Cullin1 activity or its interaction with NLRP3 to influence inflammasome activation appropriately.

6. Positive Regulators of NLRP3 Inflammasome

While most ubiquitin ligases negatively regulate NLRP3 inflammasome activation, some promote its activation. These positive regulators play crucial roles in ensuring a timely and adequate inflammatory response, highlighting the complex and balanced nature of NLRP3 regulation [113]. Understanding the role of positive regulators in inflammasome dynamics and their implications for immune responses and disease is crucial to a better understanding of inflammasome dynamics.

6.1 Pellino2

Pellino2, a member of the Pellino family of E3 ubiquitin ligases, plays a crucial role in regulating the NLRP3 inflammasome [114]. Unlike many other E3 ligases that negatively regulate NLRP3, Pellino2 acts as a positive regulator, specifically during the priming phase of inflammasome activation [115]. It contains a RING-like domain that confers its ubiquitin ligase activity, allowing it to catalyze the addition of K63-linked polyubiquitin chains to NLRP3 [93,114]. The K63-linked ubiquitination facilitated by Pellino2 is crucial for NLRP3 inflammasome activation. This type of ubiquitination, unlike K48-linked ubiquitination which typically targets proteins for degradation, is involved in regulating protein interactions and signaling pathways [13]. By adding these ubiquitin chains, Pellino2 enhances NLRP3's ability to oligomerize and assemble into the inflammasome complex. This promotes the activation of NLRP3, leading to the cleavage of pro-caspase-1 and the subsequent maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 [116].

Pellino2's activity is particularly important in response to pathogenic infections and other danger signals, ensuring a rapid and robust activation of the NLRP3 inflammasome [114]. Its expression and activity are regulated by various signaling pathways, including those activated by Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs). This regulation ensures that Pellino2 activity is tightly controlled and context dependent [115].

Experimental evidence has shown that Pellino2 deficiency results in impaired NLRP3 inflammasome activation and reduced levels of IL-1β and IL-18, while its overexpression enhances NLRP3 activation and cytokine production [117]. Importantly, Pellino2 is not involved in TLR-induced NLRP3 and pro-IL-1β upregulation at the priming stage, suggesting its role is specific to the K63-linked ubiquitination of NLRP3 during the priming phase [50].

Given its role in promoting NLRP3 inflammasome activation, dysregulation of Pellino2 could contribute to inflammatory diseases characterized by excessive or chronic inflammation. Targeting Pellino2 activity might offer a novel approach to modulating NLRP3 inflammasome activation, with potential applications in boosting immune responses or reducing pathological inflammation in various disorders.

6.2 TRAF6

Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF6) is a crucial adaptor protein and E3 ubiquitin ligase that plays a key role in regulating the activation of the NLRP3 inflammasome, a multiprotein complex central to inflammatory responses [118]. TRAF6 directly interacts with NLRP3, catalyzing the addition of K63-linked ubiquitin chains, which promotes signaling processes rather than protein degradation [118,119]. Unlike some E3 ligases that negatively regulate NLRP3, TRAF6 enhances its activation by promoting oligomerization and assembly of the inflammasome complex [77].

TRAF6 is involved in multiple aspects of NLRP3 regulation. It participates in the priming step by mediating NF-κB activation, leading to increased expression of NLRP3 and pro-IL-1β [120]. Additionally, TRAF6 promotes the formation of ASC specks, which are crucial for inflammasome assembly and activation. It can also induce mitochondrial reactive oxygen species (ROS) production, a known activator of the NLRP3 inflammasome [121,122].

The TRAF6-mediated activation of the NLRP3 inflammasome is particularly important in response to microbial infections and danger signals. TRAF6's activity and expression are regulated by upstream signaling molecules and receptors, including Toll-like receptors (TLRs) and interleukin-1 receptor (IL-1R), which recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [45]. Experimental evidence shows that knockdown or inhibition

of TRAF6 impairs NLRP3 inflammasome activation, while its overexpression enhances inflammasome activity and cytokine production [123].

The positive regulation of NLRP3 inflammasome by TRAF6 is crucial for immune responses to certain pathogens and plays a role in the development of autoimmune diseases [123]. Dysregulation of TRAF6 can contribute to various inflammatory and autoimmune conditions, such as rheumatoid arthritis, atherosclerosis, and neuroinflammatory diseases [124]. Understanding the TRAF6-NLRP3 interaction holds significant therapeutic potential, as modulating TRAF6 activity could help control NLRP3-mediated inflammation in various disease contexts [125].

7. Deubiquitinating Enzymes in NLRP3 Inflammasome Regulation

While ubiquitin ligases play a crucial role in modulating NLRP3 inflammasome activity through the addition of ubiquitin chains, the removal of these chains is equally important for the precise regulation of this complex [126]. Deubiquitinating enzymes (DUBs) are specialized proteases that cleave ubiquitin moieties from substrate proteins, thereby reversing the actions of ubiquitin ligases. In the context of the NLRP3 inflammasome, DUBs can either enhance or suppress inflammasome activation by removing specific types of ubiquitin modifications [77,105]. The dynamic interplay between ubiquitination and deubiquitination ensures a balanced and timely response to inflammatory signals, maintaining immune homeostasis and preventing excessive inflammation [127]. In the following sections, we will discuss key deubiquitinating enzymes involved in the regulation of the NLRP3 inflammasome and their mechanisms of action.

7.1 BRCC3

BRCA1/BRCA2-containing complex subunit 3 (BRCC3) is a crucial deubiquitinating enzyme that plays a significant role in regulating the NLRP3 inflammasome, a key component of the innate immune response [128]. As a member of the JAB1/MPN/Mov34 Metalloenzyme (JAMM) family of zinc-dependent metalloproteases, BRCC3 specifically cleaves K63-linked polyubiquitin chains from NLRP3, acting as a positive regulator of inflammasome activation [129]. This function is particularly important in the context of inflammatory responses and immune regulation.

BRCC3 is a component of the BRCC36 isopeptidase complex (BRISC), which is involved in various cellular processes, including DNA repair and maintenance of genomic stability [130]. In its role regulating the NLRP3 inflammasome, BRCC3 directly interacts with NLRP3, removing K63-linked ubiquitin chains from its LRR region [129]. This deubiquitination event is crucial for NLRP3 assembly and activation, facilitating the formation of the inflammasome complex and subsequent activation of caspase 1. The process leads to the production and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 [13].

The timing of BRCC3's action is specific, occurring after the priming step but before or during the activation step of NLRP3 inflammasome formation [48]. This mechanism ensures that NLRP3 activation is timely and appropriately scaled, preventing unwarranted inflammation while allowing for an effective immune response when needed. BRCC3's activity has been observed in various cell types, including macrophages and dendritic cells, underscoring its importance in diverse immune contexts [131].

The regulation of NLRP3 by BRCC3 has significant implications for both physiological and pathological processes [47]. Proper functioning of BRCC3 is essential for the immune system's ability to respond to infections and tissue damage. However, dysregulation of BRCC3 activity can lead to either insufficient or excessive inflammasome activation, potentially contributing to a range of inflammatory disorders [128]. Conditions such as autoinflammatory syndromes, chronic inflammatory diseases, and certain cancers have been associated with aberrant NLRP3 activation, highlighting the importance of BRCC3 in maintaining immune homeostasis [1].

The therapeutic potential of targeting BRCC3 and its regulatory pathways is significant. Modulating BRCC3 activity could be beneficial in treating diseases characterized by excessive inflammasome activation, such as gout, atherosclerosis, and autoimmune disorders. Inhibiting BRCC3 could potentially dampen NLRP3 inflammasome activation in conditions with excessive inflammation. Conversely, enhancing BRCC3 activity might improve immune responses in situations where NLRP3 activation is deficient [78].

7.2 USP7

Ubiquitin-specific peptidase 7 (USP7), also known as Herpesvirus-associated ubiquitin-specific protease (HAUSP), is a crucial deubiquitinating enzyme that plays a significant role in regulating the NLRP3 inflammasome [132]. As a member of the ubiquitin-specific protease (USP) family, USP7 removes ubiquitin moieties from substrate proteins, rescuing them from proteasomal degradation or altering their functional state [133]. This cysteine protease has diverse cellular functions, including roles in DNA damage response, apoptosis, and immune regulation.

In the context of NLRP3 inflammasome regulation, USP7 directly interacts with NLRP3 and modulates its stability and activity through deubiquitination [134]. It primarily removes K48-linked polyubiquitin chains, which are typically associated with targeting proteins for proteasomal degradation. By deubiquitinating NLRP3, USP7 stabilizes the protein and enhances its accumulation within the cell. This mechanism counteracts the effects of various E3 ubiquitin ligases, such as TRIM31, MARCH7, and FBXL2, which target NLRP3 for degradation [134].

USP7 acts as a positive regulator of the NLRP3 inflammasome [135]. By preventing the degradation of NLRP3, USP7 increases the availability of this protein, thereby promoting the formation and activation of the inflammasome complex [135]. This leads to the subsequent activation of caspase-1 and the maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 [136]. The stabilization of NLRP3 by USP7 ensures a robust inflammatory response to effectively combat infections or promote tissue repair.

The activity of USP7 in regulating NLRP3 has been observed in various cell types, including macrophages and other immune cells [13]. USP7 displays specificity for NLRP3 among various inflammasome components, underscoring its targeted regulatory role. It does not significantly affect other key inflammasome proteins like ASC or Procaspase-1, focusing its activity primarily on NLRP3 [137].

Experimental evidence supports USP7's role in NLRP3 regulation. A study showed that the inhibition or knockdown of USP7 leads to decreased NLRP3 protein levels and reduced inflammasome activation [47]. Conversely, overexpression of USP7 results in increased NLRP3 stability and enhanced inflammasome activity, corroborating its role as a positive regulator.

The activity and expression of USP7 itself are subject to regulation, which can influence its effect on the NLRP3 inflammasome. Various factors, including post-translational modifications and protein-protein interactions, regulate USP7's activity. These regulatory mechanisms can indirectly affect NLRP3 inflammasome activation [135].

Given its role in promoting NLRP3 activation, dysregulation of USP7 could contribute to inflammatory disorders characterized by excessive or chronic NLRP3 activation. Conditions such as autoinflammatory diseases, metabolic disorders, and certain infections might be influenced by alterations in USP7 activity [138]. This makes USP7 a potential therapeutic target for managing NLRP3-related inflammatory diseases. Modulating USP7 activity, possibly using USP7 inhibitors, could be a strategy to control NLRP3-mediated inflammation [139].

USP7 functions within a broader network of NLRP3 regulators, including other deubiquitinating enzymes and ubiquitin ligases. Understanding how USP7 interacts with these other factors is crucial for a comprehensive view of NLRP3 regulation. The balance between ubiquitination by E3 ligases and deubiquitination by DUBs like USP7 allows for fine-tuning of NLRP3 levels and activity, which is crucial for maintaining appropriate inflammatory responses while preventing excessive inflammation [77].

7.3 USP47

USP47, a member of the ubiquitin-specific protease family, plays a crucial role in regulating the NLRP3 inflammasome, a key component of the innate immune response. This deubiquitinating enzyme acts by removing ubiquitin moieties from NLRP3, preventing its proteasomal degradation and increasing its stability within the cell [140]. Through this mechanism, USP47 functions as a positive regulator of NLRP3 inflammasome activation, enhancing the availability of this key component and promoting its assembly into the active inflammasome complex [135].

The deubiquitinating activity of USP47 facilitates efficient inflammasome assembly by allowing NLRP3 to interact with the adaptor protein ASC and Pro-caspase 1 [45]. This process is essential for a robust inflammatory response, enabling cells to effectively respond to pathogenic infections and other danger signals [141]. USP47 displays specificity for NLRP3 among various inflammasome components, underscoring its targeted regulatory role [21]. Its activity is particularly significant in contexts where enhanced inflammasome activation is required, such as during microbial infections, tissue damage, or sterile inflammation.

Experimental study has demonstrated that inhibition or knockdown of USP47 leads to reduced NLRP3 protein levels and diminished inflammasome activation, while overexpression results in increased NLRP3 stability and enhanced inflammasome activity [47]. These findings suggest that USP47 is critical for maintaining appropriate levels of NLRP3 to ensure effective inflammasome responses. Given its role in promoting NLRP3 activation, dysregulation of USP47 could contribute to inflammatory disorders characterized by excessive or chronic NLRP3 activation, such as autoinflammatory diseases, metabolic disorders, and certain infections [142].

Targeting USP47 offers a promising therapeutic approach for managing NLRP3-related inflammatory diseases. Inhibiting USP47 might help reduce excessive inflammation in conditions where NLRP3 hyperactivation is detrimental, while enhancing its activity could boost NLRP3 responses when a stronger immune response is needed [135]. USP47 functions within a complex network of NLRP3 regulators, including other deubiquitinating enzymes and ubiquitin ligases.

7.4 A20

A20, also known as Tumor Necrosis Factor Alpha-Induced Protein 3 (TNFAIP3), is a pivotal anti-inflammatory molecule that plays a crucial role in regulating immune and inflammatory responses, including the NLRP3 inflammasome [143]. As a ubiquitin-editing enzyme with both deubiquitinating (DUB) and E3 ubiquitin ligase activities, A20 possesses a unique dual functionality that allows it to modulate protein ubiquitination status in complex ways, making it a versatile regulator of various signaling pathways [144].

In the context of NLRP3 inflammasome regulation, A20 primarily functions as a negative regulator, helping to prevent excessive or prolonged inflammatory responses. Its mechanism of action involves the removal of K63-linked polyubiquitin chains from NLRP3 and potentially other inflammasome components [143]. This deubiquitination is

crucial for controlling the activation and assembly of the NLRP3 inflammasome, as it interferes with the recruitment of downstream signaling molecules necessary for inflammasome assembly. By maintaining NLRP3 in an inactive state under normal conditions, A20 prevents unwarranted inflammasome activation and excessive inflammation [145].

The importance of A20 in regulating the NLRP3 inflammasome is underscored by an experimental study showing that the absence or inhibition of A20 leads to enhanced NLRP3 inflammasome activation and increased production of pro-inflammatory cytokines such as IL-1β and IL-18 [146]. Conversely, overexpression of A20 results in reduced NLRP3 activity and dampened inflammatory responses. These findings highlight the critical role of A20 in maintaining the balance between activation and inhibition of the NLRP3 inflammasome [147].

A20's regulatory effects extend beyond the NLRP3 inflammasome, as it also modulates other signaling pathways involved in immune responses, such as NF-κB and mitogen-activated protein kinase (MAPK) [147]. This multifaceted regulation allows A20 to integrate various signals and coordinate an appropriate immune response [148]. By inhibiting NF-κB signaling, A20 can reduce the transcription of pro-inflammatory cytokines and NLRP3 itself, further dampening the inflammatory response. This interplay between A20 and multiple signaling pathways adds another layer of complexity to its role in inflammation and immunity [149].

The impact of A20 on NLRP3 inflammasome activation may vary depending on the cell type and specific inflammatory context. This cell type-specific effect adds another layer of complexity to its regulatory role and highlights the need for further research to fully understand the nuances of A20's function in different cellular environments [150].

Given its central role in regulating inflammation, A20 represents a potential therapeutic target for various inflammatory and autoimmune diseases. Enhancing A20 activity could be beneficial in conditions characterized by excessive NLRP3 activation, such as rheumatoid arthritis, systemic lupus erythematosus, and certain autoinflammatory syndromes [151]. Therapeutic strategies aimed at modulating A20 function may help restore immune homeostasis and alleviate disease symptoms. By controlling the ubiquitination status of NLRP3 and other signaling molecules, A20 helps maintain immune homeostasis and prevent chronic inflammatory responses [152]. Understanding the mechanisms by which A20 regulates the NLRP3 inflammasome and developing strategies to modulate its activity holds significant therapeutic potential for managing inflammatory and autoimmune diseases.

8. Degradation of Ubiquitinated NLRP3

The ubiquitination of NLRP3 plays a critical role in regulating its activation and degradation [45]. Ubiquitination involves the attachment of ubiquitin molecules to lysine residues on NLRP3, which can lead to different cellular outcomes depending on the type of ubiquitin linkage [66]. Specifically, K48-linked ubiquitination of NLRP3 typically targets it for proteasomal degradation. E3 ubiquitin ligases such as TRIM31 and MARCH7 have been shown to mediate K48-linked polyubiquitination of NLRP3, promoting its degradation via the proteasome and thereby inhibiting inflammasome activation [85,153]. On the other hand, K63-linked ubiquitination is associated with autophagic degradation [77]. This process involves the interaction of ubiquitinated NLRP3 with autophagic adaptors like p62, which facilitate its delivery to the autophagosome for degradation [98,154]. The balance between these ubiquitination pathways ensures that NLRP3 levels are tightly regulated, preventing excessive inflammasome activation that could lead to pathological inflammation [54].

9. Pathogens Hijack Host Ubiquitination Pathway to Regulate NLRP3 Inflammasome Activation

Pathogens have evolved sophisticated strategies to manipulate host cellular pathways to evade immune responses and establish infections. One such strategy involves hijacking the host ubiquitination pathway to regulate NLRP3 inflammasome activation [155]. Ubiquitination, a post-translational modification where ubiquitin proteins are attached to target proteins, plays a crucial role in controlling the stability, localization, and activity of many cellular proteins, including those involved in immune responses [156]. Below Table 1 (Ref. [94,157–188]) depicts various pathogen strategies for modulating ubiquitination to influence inflammasome activation.

9.1 Bacterial Pathogens

Intracellular bacteria have evolved diverse strategies to manipulate the host ubiquitination pathway and regulate NLRP3 inflammasome activation (Fig. 2) [189,190]. Mycobacterium tuberculosis employs protein tyrosine phosphatase A (PtpA) as a deubiquitinase to remove K63-linked ubiquitin chains from NLRP3, inhibiting its activation, reducing IL-1β production and dampening the host immune response [191,192]. while its zinc metalloprotease 1 (Zmp1) interferes with the K63-linked ubiquitination of Pro-IL-1β, preventing its maturation and secretion [193]. This further suppresses the inflammatory response. Yersinia species use a type III secretion system to inject effector proteins like Yersinia outer protein J/P (YopJ/YopP) and Yersinia outer protein M (YopM) into host cells [194]. Acetyltransferases like YopJ/YopP inhibits the activation of NF-κB and MAPK pathways, which are crucial for NLRP3 priming [195]. It also interferes with the ubiquitination of TRAF proteins, further suppressing inflammatory signaling. YopM recruits host cysteine protease USP7 to deubiquitinate NLRP3, leading to its destabilization and degradation [196]. Shigella flexneri uses IpaH family pro-

Table 1. Pathogen strategies for modulating ubiquitination to influence inflammasome activation.

Pathogen type	Pathogen	Effector proteins	Ubiquitination mechanism and effect	Mechanism of action	Target pathway/Sensor
Bacterial pathogens	Mycobacterium tuberculosis	PtpA	Deubiquitinase activity	Removes K63-linked ubiquitin chains from NLRP3, inhibiting activation and reducing IL-1β production.	NLRP3 [157]
		Zmp1	Interferes with ubiquitination	Interferes with K63-linked ubiquitination of pro-IL-1β, preventing its maturation and secretion.	Pro-IL-1β [158]
	Yersinia species	YopJ/YopP	Inhibits ubiquitination	Inhibits NF-κB and MAPK pathways, interfering with NLRP3 priming and ubiquitination of TRAF proteins.	NF-κB, MAPK [159]
		YopM	Recruits deubiquitinase USP7	Recruits USP7 to deubiquitinate NLRP3, leading to its destabilization and degradation.	NLRP3 [160]
	Shigella flexneri	IpaH proteins (e.g., IpaH7.8)	E3 ubiquitin ligase activity	Targets NLRP3 inflammasome components for degradation, enhancing inflammasome activation.	GLMN [161]
	Listeria monocytogenes	LLO	Modulates ubiquitination pathways	Induces K^+ efflux, modulating NLRP3 activation and manipulating host ubiquitination pathways.	NLRP3 [162]
		InlC	Interacts with ubiquitination-related signaling	Interacts with IKKα, affecting NF-κB signaling and indirectly influencing NLRP3 inflammasome priming.	NF-κB [94]
	Brucella abortus	TcpB	Interferes with ubiquitination-related signaling	Mimics TIRAP/Mal, interfering with TLR signaling pathways and reducing NLRP3 inflammasome activation.	TLR signaling [163]
	Pseudomonas aeruginosa	Various effectors	Disrupt host ubiquitination processes	Disrupt host cell signaling and ubiquitination processes, indirectly affecting NLRP3 inflammasome activation.	NLRP3 [164,165]
	Legionella pneumophila	LubX	E3 ubiquitin ligase activity	Targets host kinase CLK1, affecting cellular processes including inflammasome regulation.	NLRP3 [166]

Table 1. Continued.

Pathogen type	Pathogen	Effector proteins	Ubiquitination mechanism and effect	Mechanism of action	Target pathway/Sensor
	Salmonella enterica	SseL	Deubiquitinase activity	Removes K63-linked ubiquitin chains from host proteins, potentially affecting NLRP3 inflammasome activation.	NLRP3 [167]
	Francisella tularensis	Indirect modulation of ubiquitination pathways	Indirect modulation of ubiquitination pathways	Prostaglandin E2 production inhibits NLRP3 inflammasome activation by interfering with potassium efflux.	NLRP3 [168]
	Rickettsia species	Sca proteins	Interacts with host ubiquitin ligases	Interact with host ubiquitin ligases, modulating cellular processes including inflammasome regulation.	NLRP3 [169]
	Coxiella burnetii	Dot/Icm type IV secretion system	Injects effector proteins to modulate host ubiquitination pathways	Injects effector proteins to modulate host cell processes including ubiquitination pathways.	NLRP3 [170]
	Streptococcus pyogenes	SpeB, Streptolysin O	Degrades ubiquitination-related host proteins	Degrades host proteins involved in inflammasome activation, modulating NLRP3 inflammasome activation.	NLRP3 [171,172]
	Porphyromonas gingivalis	Gingipains	Degrades ubiquitination-related host proteins	Degrade multiple host proteins, potentially affecting NLRP3 components.	NLRP3 [173,174]
	Neisseria gonorrhoeae	Opa proteins	Modulates ubiquitination-related signaling	Interact with host receptors and modulate signaling pathways.	NLRP3 [175]
	Borrelia burgdorferi	OspA, OspB	Potentially modulates ubiquitination-related signaling	Interact with host cells, potentially modulating inflammasome activation.	NLRP3 [176,177]
Viral Pathogens	Influenza A Virus	NS1	Interacts with TRIM25, an E3 ubiquitin ligase	Inhibits RIG-I ubiquitination and subsequent antiviral signaling.	RIG-I [177]
	Hepatitis C Virus	NS3/4A	Cleaves MAVS and interacts with Parkin, affecting ubiquitination pathways	Cleaves MAVS and interacts with Parkin, affecting ubiquitination pathways.	MAVS [178]
	Dengue Virus	NS3, NS2B3	Cleaves ubiquitination-related proteins STING and cGAS	Cleaves STING and targets cGAS for degradation, disrupting innate immune signaling.	STING, cGAS [179]
	Human Papillomavirus	E6	Recruits E6AP, an E3 ubiquitin ligase	Recruits E6AP, targeting p53 for degradation.	p53 [180]

Table 1. Continued.

Pathogen type	Pathogen	Effector proteins	Ubiquitination mechanism and effect	Mechanism of action	Target pathway/Sensor
	Epstein-Barr Virus	BPLF1	Deubiquitinase activity	Deubiquitinates TRAF6 and NEMO, suppressing NF-κB signaling.	TRAF6, NEMO [181]
	Kaposi's Sarcoma-associated Herpesvirus	ORF64, K5	Viral deubiquitinase and E3 ubiquitin ligase activity	Suppresses RIG-I-mediated signaling and targets host immune proteins for degradation.	RIG-I [182]
	Enterovirus 71	3C protease	Cleaves ubiquitination-related protein TRIM25	Cleaves TRIM25, inhibiting RIG-I-mediated antiviral signaling.	TRIM25 [183]
	Human Cytomegalovirus	pUL26, pUL48	Interferes with ubiquitination-related NF-κB activation and acts as a deubiquitinase	Interferes with NF-κB activation and acts as a deubiquitinase.	NF-κB [184]
	Herpes Simplex Virus	ICP0	E3 ubiquitin ligase activity	Targets various host proteins for degradation.	NLRP3 [185]
	Measles Virus	V protein	Interacts with multiple host factors affecting ubiquitination processes	Interacts with multiple host factors affecting ubiquitination processes.	NLRP3 [186]
	Nipah Virus	W protein	Inhibits ubiquitination-related RIG-I-like receptor signaling	Inhibits RIG-I-like receptor signaling.	RIG-I-like receptors [187]
	Crimean-Congo Hemorrhagic Fever Virus	L protein	Deubiquitinase activity		[188]

PtpA, protein tyrosine phosphatase A; Zmp1, zinc metalloproteinase 1; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, interleukin 1 beta; USP7, ubiquitin-specific peptidase 7; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK, mitogen-activated protein kinase; TRAF, TNF receptor-associated factor; IKKα, inhibitor of nuclear factor kappa-B kinase subunit alpha; TIRAP, Toll/IL-1 receptor domain-containing adapter protein; TLR, Toll-like receptor; CLK1, clock homolog 1; GLMN, gliomedin; YopJ/YopP, Yersinia outer protein J/P; YopM, Yersinia outer protein M; IpaH, invasion plasmid antigen H; LLO, listeriolysin O; InlC, internalin C; TcpB, tip component of the type III secretion system; LubX, a type III effector from Listeria; SseL, Salmonella secreted effector L; OspA, outer secreted protein A; OspB, outer secreted protein B; NS1, non-structural protein 1; NS3/4A, non-structural proteins 3 and 4A; NS3, non-structural protein 3; NS2B3, non-structural protein 2B and 3; TRIM25, tripartite motif-containing protein 25; MAVS, mitochondrial antiviral signaling protein; STING, stimulator of interferon genes; cGAS, cyclic GMP-AMP synthase; RIG-I, retinoic acid-inducible gene I; BPLF1, bacteriophage-like protein 1; ORF64, open reading frame 64; pUL26, protein UL26; ICP0, infected cell protein 0; E6AP, E6 associated protein; NEMO, NF-κB essential modulator; MAVS; mitochondrial antiviral signaling protein.

teins as E3 ubiquitin ligases to target NLRP3 inflammasome components for degradation, like IpaH7.8 ubiquitinates gliomedin (GLMN), a negative regulator of NLRP3, leading to its degradation and enhancing inflammasome activation [161,197]. Listeria monocytogenes utilizes Listeriolysin O (LLO) and InlC to modulate host ubiquitination and NF-κB signaling [198]. LLO is a pore-forming toxin that can induce K^+ efflux, activating the NLRP3 inflammasome. However, Listeria also uses LLO to manipulate host ubiquitination pathways, potentially modulating its activation [199–201]. Further its effector InlC interacts with IKKα, affecting NF-κB signaling and indirectly influencing NLRP3 inflammasome priming [202]. Chlamydia trachomatis employs Chlamydia deubiquitinating enzyme 1 (ChlaDub1) to deubiquitinate NF-κB and CT441 to degrade p65 [203]. TIR domain-containing protein B (TcpB) from Brucella abortus mimics the host adaptor protein TIRAP/Mal, interfering with TLR signaling pathways

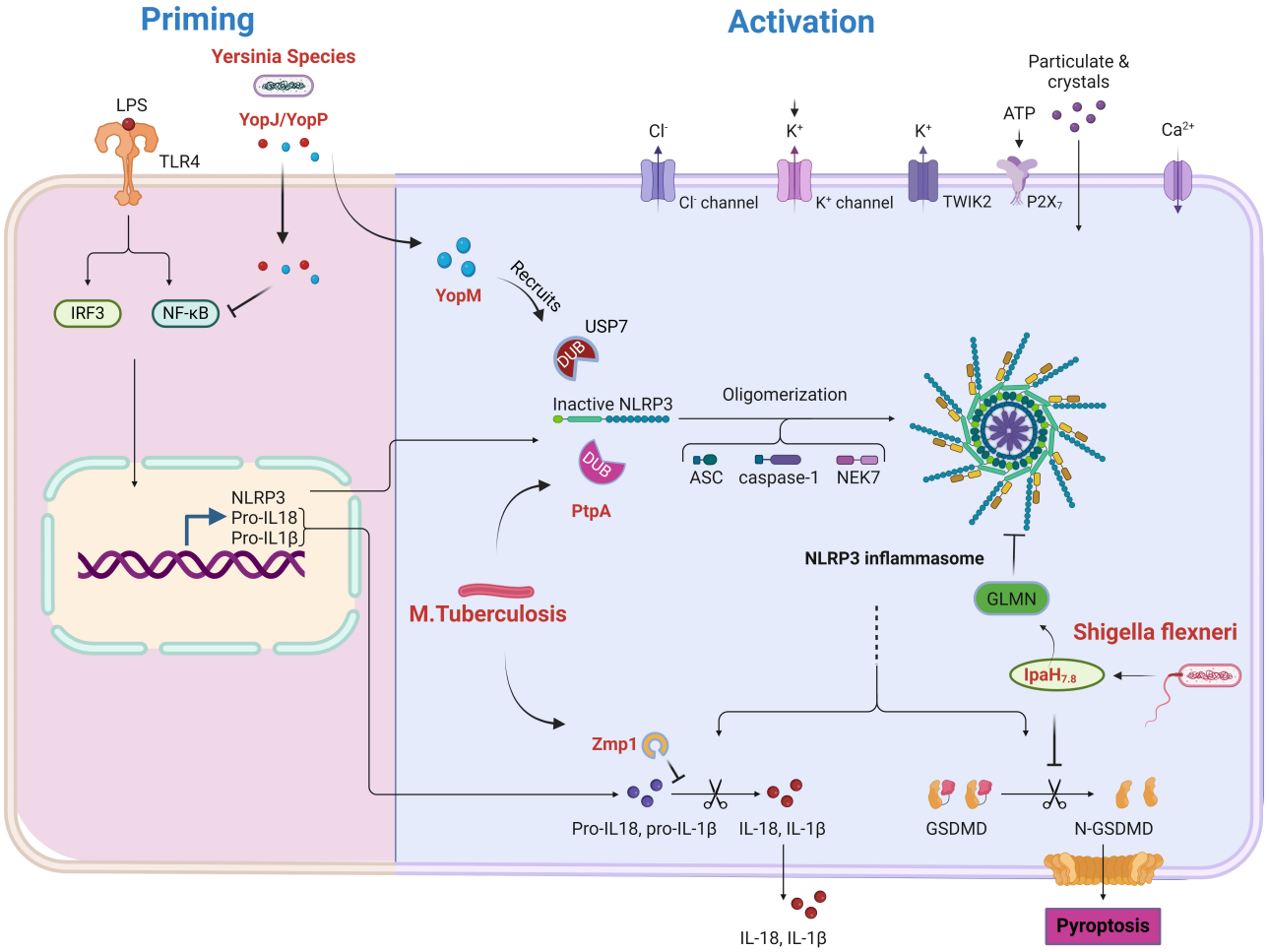

Fig. 2. Modulation of NLRP3 inflammasome priming and activation by bacterial pathogens. This figure depicts how bacterial pathogens influence NLRP3 inflammasome priming and activation. During priming, lipopolysaccharide (LPS) triggers TLR4, leading to NF-κB and IRF3 activation, which upregulates NLRP3, pro-IL-1β, and pro-IL-18. Yersinia species inhibit this process using YopJ/YopP. In the activation phase, ion fluxes (Cl^-, K^+, Ca^{2+}) are crucial. Yersinia species use YopM to recruit USP7, stabilizing NLRP3. Mycobacterium tuberculosis utilizes PtpA to deubiquitinate NLRP3 and Zmp1 to hinder pro-IL-1β maturation. Inflammasome assembly involves NLRP3, ASC, caspase-1, and NEK7. Shigella flexneri uses IpaH7.8 to degrade inflammasome components, promoting activation. Activated caspase-1 processes pro-IL-1β and pro-IL-18 and cleaves gasdermin D (GSDMD), leading to pyroptosis. Created using BioRender.com.

[204]. By blocking the proper recruitment of signaling proteins and inhibiting NF-κB and MAPK pathways, TcpB disrupts the transcription of pro-inflammatory genes, thereby reducing the priming and activation of the NLRP3 inflammasome [9]. This strategic interference helps Brucella abortus evade the host immune response and establish infection.

Other bacterial pathogens like Pseudomonas aeruginosa, use various effector proteins to disrupt host cell signaling and ubiquitination processes indirectly affecting NLRP3 inflammasome activation [164,165]. Legionella pneumophila, an intracellular bacterium uses its type IV secretion system to inject effector proteins like LubX, E3 ubiquitin ligase that targets the host kinase clock homolog 1 (CLK1), affecting various cellular processes including inflammasome regulation [205]. Salmonella enterica uses different effector protein like Salmonella secreted effector L (SseL), deubiquitinase that removes K63-linked ubiquitin chains from various host proteins, potentially affecting NLRP3 inflammasome activation [206]. Francisella tularensis, a highly virulent bacterium induces prostaglandin E2 production, which inhibits NLRP3 inflammasome activation by interfering with potassium efflux [207].

Surface Cell Antigen (Sca) proteins from Rickettsia species, an obligate intracellular bacteria interact with host ubiquitin ligases, modulating cellular processes including inflammasome regulation [208]. Coxiella burnetiid, intracellular bacterium injects effector proteins via its Dot/Icm type IV secretion system to modulate host cell processes including ubiquitination pathways [209]. Streptococcus pyogenes uses Streptococcal Pyrogenic Exotoxin B (SpeB), cysteine protease that degrades host proteins, including

those involved in inflammasome activation and Streptolysin O, pore-forming toxin that can modulate the NLRP3 inflammasome activation [210]. Porphyromonas gingivalis employs gingipains to degrade multiple host proteins, potentially affecting NLRP3 components [173]. Neisseria gonorrhoeae uses Opa proteins to interact with host receptors and modulate signaling pathways [211]. Borrelia burgdorferi's, the causative agent of Lyme disease uses outer surface proteins like outer secreted protein A (OspA) and outer secreted protein B (OspB) proteins to interact with host cells, potentially modulating inflammasome activation [212].

9.2 Viral Pathogens

Viruses have also developed sophisticated mechanisms to manipulate host ubiquitination and NLRP3 inflammasome activation [213]. Influenza A Virus uses its NS1 protein to interact with TRIM25, an E3 ubiquitin ligase, inhibiting the ubiquitination of RIG-I and subsequent activation of antiviral signaling pathways indirectly affecting the NLRP3 inflammasome activation [214]. Human Papillomavirus employs its E6 oncoprotein to recruit the cellular E3 ubiquitin ligase E6AP, targeting p53 for degradation [180]. Epstein-Barr Virus's BamHI fragment P leftward open reading frame 1 (BPLF1) deubiquitinates TRAF6 and NF-kappa-B Essential Modulator (NEMO), suppressing NF-κB signaling [181]. Kaposi's Sarcoma-associated Herpesvirus uses viral deubiquitinase Open Reading Frame 64 (ORF64) to suppress RIG-I-mediated signaling and viral E3 ubiquitin ligase K5 to target host immune proteins for degradation [182].

Enterovirus 71 (EV71) virus, responsible for hand, foot, and mouth disease uses its 3C protease to cleave TRIM25, inhibiting RIG-I-mediated antiviral signaling [183]. Hepatitis C Virus employs non-structural proteins 3 and 4A (NS3/4A) protease to cleave mitochondrial antiviral signaling protein (MAVS) and its core protein interacts with Parkin. Dengue Virus uses NS3 protease to cleave stimulator of interferon genes (STING) and Non-Structural Protein 2B and 3 (NS2B3) to target cyclic GMP-AMP synthase (cGAS) for degradation [215]. Human Cytomegalovirus's protein UL26 (pUL26) interferes with NF-κB activation, while pUL48 acts as a deubiquitinase [216]. Herpes Simplex Virus's infected cell protein 0 (ICP0), E3 ubiquitin ligase targets various host proteins for degradation. Measles Virus's V protein interacts with multiple host factors affecting ubiquitination processes [217]. Nipah Virus's W protein inhibits RIG-I-like receptor signaling. Crimean-Congo Hemorrhagic Fever Virus's L protein has deubiquitinase activity affecting various host processes including inflammasome regulation [218]. Chikungunya Virus's nsP2 interferes with host interferon signaling, affecting NLRP3 inflammasome activation. Zika Virus's NS3 can cleave STING, disrupting innate immune signaling [219].

9.3 Parasitic Pathogens

The NLRP3 inflammasome plays a crucial role in the innate immune response against various parasitic infections [45,78,220]. Protozoan parasites such as Plasmodium, Toxoplasma gondii, Leishmania species, and Trypanosoma cruzi, as well as helminth parasites like Schistosoma mansoni and Heligmosomoides polygyrus manipulate host ubiquitination pathways to regulate NLRP3 inflammasome activation [220–222]. In Plasmodium infections, hemozoin and parasite DNA have been identified as potent NLRP3 activators, contributing to both protective immunity and immunopathology in malaria [223,224]. Leishmania species use Glycoprotein 63 (GP63), a surface protease, to cleave and inactivate multiple host proteins involved in innate immune signaling [225,226]. Similarly, Toxoplasma gondii employs sophisticated mechanisms to modulate host cellular processes, including the regulation of the NLRP3 inflammasome [227,228]. The parasite secretes Granule Protein 16 (GRA16), a dense granule protein that interacts with the host deubiquitinase Herpesvirus-Associated Ubiquitin-Specific Protease/ Ubiquitin-Specific Peptidase 7 (HAUSP/USP7), potentially affecting p53 stability and indirectly influencing NLRP3 inflammasome activation [227,229]. This interaction highlights the complex interplay between T. gondii and host cellular pathways [224]. Concurrently, T. gondii activates the NLRP3 inflammasome through mechanisms involving potassium efflux and reactive oxygen species (ROS) production. The resulting NLRP3-dependent IL-1β production plays a crucial role in controlling T. gondii infection, demonstrating the dual nature of the parasite's interaction with host innate immune responses. These findings underscore the intricate balance between parasite survival strategies and host defense mechanisms, where T. gondii both manipulates and triggers host inflammatory pathways to establish infection while the host attempts to control parasite replication [227,230].

These diverse strategies employed by various pathogens highlight the complex interplay between host defense mechanisms and pathogen evasion tactics, centered around the manipulation of the ubiquitination system and NLRP3 inflammasome activation [189].

10. Conclusions and Future Perspective

The regulation of the NLRP3 inflammasome through ubiquitin ligases and deubiquitinating enzymes represents a sophisticated and tightly regulated system essential for maintaining immune balance [105]. This review has elucidated the complex network of both positive and negative regulators that modulate NLRP3 inflammasome activity through diverse ubiquitination and deubiquitination processes. The roles of E3 ubiquitin ligases, such as TRIM31, MARCH7, FBXL2, and Pellino2, alongside deubiquitinating enzymes like BRCC3, USP7, and A20, highlight the intricate nature of this regulatory system [105]. These enzymes collectively influence NLRP3 protein levels, stabil-

ity, and activation, thereby affecting the magnitude and duration of inflammatory responses. In the context of intracerebral hemorrhage (ICH), where excessive inflammation contributes to secondary brain injury, understanding these regulatory mechanisms offers insights into potential therapeutic strategies [36]. Edaravone, for instance, may modulate the activity of specific ubiquitin ligases, potentially attenuating inflammasome-driven inflammation and providing a novel approach to managing ICH [42].

Furthermore, pathogens' ability to exploit and manipulate the host's ubiquitination machinery to evade immune detection adds another layer of complexity. Various bacteria, viruses, and parasites have developed advanced strategies to disrupt NLRP3 inflammasome activation by targeting key components of the ubiquitination pathway [191]. This interplay exemplifies the evolutionary battle between host defense mechanisms and pathogen evasion tactics, revolving around post-translational modifications.

Understanding these regulatory mechanisms offers valuable insights into the fundamental aspects of inflammation and presents potential therapeutic opportunities for inflammatory and infectious diseases. The delicate balance between NLRP3 inflammasome activation and inhibition, governed by ubiquitination and deubiquitination, presents both challenges and prospects for targeted interventions.

However, several questions remain for future investigation:

1. How do distinct ubiquitination patterns on NLRP3 influence its function and activation kinetics?
2. What are the specific molecular mechanisms by which pathogens disrupt host ubiquitination machinery to modulate NLRP3 inflammasome activation?
3. How do cell type-specific variations in ubiquitin ligase and deubiquitinase expression impact NLRP3 inflammasome regulation across different tissues and disease states?
4. Can targeting specific ubiquitin ligases or deubiquitinases provide effective and selective treatments for inflammatory diseases while preserving overall immune function?
5. How do environmental factors and cellular stress affect the activity of ubiquitin ligases and deubiquitinases in the context of NLRP3 inflammasome regulation?
6. What is the role of interactions between ubiquitination and other post-translational modifications in fine-tuning NLRP3 inflammasome activation?

Addressing these questions will enhance our understanding of NLRP3 inflammasome regulation and could lead to innovative therapeutic strategies for managing inflammatory disorders and combating infectious diseases.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this work the author used ChatGPT in order to check spell and grammar. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Author Contributions

SB was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author acknowledges many investigators in the field whose primary data could not be cited in this review because of space limitations. Figures were created with BioRender.com.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest.

References

[1] Zheng D, Liwinski T, Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. Cell Discovery. 2020; 6: 36.

[2] Schroder K, Tschopp J. The inflammasomes. Cell. 2010; 140: 821–832.

[3] Martinon F, Tschopp J. Inflammatory caspases and inflammasomes: master switches of inflammation. Cell Death and Differentiation. 2007; 14: 10–22.

[4] Sutterwala FS, Ogura Y, Flavell RA. The inflammasome in pathogen recognition and inflammation. Journal of Leukocyte Biology. 2007; 82: 259–264.

[5] Lamkanfi M, Vande Walle L, Kanneganti TD. Deregulated inflammasome signaling in disease. Immunological Reviews. 2011; 243: 163–173.

[6] Davis BK, Wen H, Ting JPY. The inflammasome NLRs in immunity, inflammation, and associated diseases. Annual Review of Immunology. 2011; 29: 707–735.

[7] Kufer TA, Fritz JH, Philpott DJ. NACHT-LRR proteins (NLRs) in bacterial infection and immunity. Trends in Microbiology. 2005; 13: 381–388.

[8] Martinon F, Tschopp J. NLRs join TLRs as innate sensors of pathogens. Trends in Immunology. 2005; 26: 447–454.

[9] Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 Inflammasome Pathway: A Review of Mechanisms and Inhibitors for the Treatment of Inflammatory Diseases. Frontiers in Aging Neuroscience. 2022; 14: 879021.

[10] Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. International Journal of Molecular Sciences. 2019; 20: 3328.

[11] Bryant C, Fitzgerald KA. Molecular mechanisms involved in inflammasome activation. Trends in Cell Biology. 2009; 19: 455–464.
[12] Sharma BR, Kanneganti TD. NLRP3 inflammasome in cancer and metabolic diseases. Nature Immunology. 2021; 22: 550–559.
[13] Xu J, Núñez G. The NLRP3 inflammasome: activation and regulation. Trends in Biochemical Sciences. 2023; 48: 331–344.
[14] de Zoete MR, Palm NW, Zhu S, Flavell RA. Inflammasomes. Cold Spring Harbor Perspectives in Biology. 2014; 6: a016287.
[15] Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. Cell. 2004; 117: 561–574.
[16] Dai Y, Zhou J, Shi C. Inflammasome: structure, biological functions, and therapeutic targets. MedComm. 2023; 4: e391.
[17] Sundaram B, Tweedell RE, Prasanth Kumar S, Kanneganti TD. The NLR family of innate immune and cell death sensors. Immunity. 2024; 57: 674–699.
[18] Zaki MH, Boyd KL, Vogel P, Kastan MB, Lamkanfi M, Kanneganti TD. The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. Immunity. 2010; 32: 379–391.
[19] Mi L, Min X, Chai Y, Zhang J, Chen X. NLRP1 Inflammasomes: A Potential Target for the Treatment of Several Types of Brain Injury. Frontiers in Immunology. 2022; 13: 863774.
[20] Wen J, Xuan B, Liu Y, Wang L, He L, Meng X, *et al*. Updating the NLRC4 Inflammasome: from Bacterial Infections to Autoimmunity and Cancer. Frontiers in Immunology. 2021; 12: 702527.
[21] Christgen S, Place DE, Kanneganti TD. Toward targeting inflammasomes: insights into their regulation and activation. Cell Research. 2020; 30: 315–327.
[22] Rathinam VAK, Jiang Z, Waggoner SN, Sharma S, Cole LE, Waggoner L, *et al*. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nature Immunology. 2010; 11: 395–402.
[23] Sharma BR, Karki R, Kanneganti TD. Role of AIM2 inflammasome in inflammatory diseases, cancer and infection. European Journal of Immunology. 2019; 49: 1998–2011.
[24] Loeven NA, Medici NP, Bliska JB. The pyrin inflammasome in host-microbe interactions. Current Opinion in Microbiology. 2020; 54: 77–86.
[25] Park YH, Wood G, Kastner DL, Chae JJ. Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nature Immunology. 2016; 17: 914–921.
[26] Carriere J, Dorfleutner A, Stehlik C. NLRP7: From inflammasome regulation to human disease. Immunology. 2021; 163: 363–376.
[27] Elinav E, Strowig T, Kau AL, Henao-Mejia J, Thaiss CA, Booth CJ, *et al*. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell. 2011; 145: 745–757.
[28] Khare S, Dorfleutner A, Bryan NB, Yun C, Radian AD, de Almeida L, *et al*. An NLRP7-containing inflammasome mediates recognition of microbial lipopeptides in human macrophages. Immunity. 2012; 36: 464–476.
[29] Ranson N, Kunde D, Eri R. Regulation and Sensing of Inflammasomes and Their Impact on Intestinal Health. International Journal of Molecular Sciences. 2017; 18: 2379.
[30] Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nature Reviews. Microbiology. 2009; 7: 99–109.
[31] Newton K, Strasser A, Kayagaki N, Dixit VM. Cell death. Cell. 2024; 187: 235–256.
[32] Jo EK, Kim JK, Shin DM, Sasakawa C. Molecular mechanisms regulating NLRP3 inflammasome activation. Cellular & Molecular Immunology. 2016; 13: 148–159.
[33] Kanneganti TD, Lamkanfi M, Núñez G. Intracellular NOD-like receptors in host defense and disease. Immunity. 2007; 27: 549–559.
[34] Wang Z, Zhang S, Xiao Y, Zhang W, Wu S, Qin T, *et al*. NLRP3 Inflammasome and Inflammatory Diseases. Oxidative Medicine and Cellular Longevity. 2020; 2020: 4063562.
[35] Man SM, Kanneganti TD. Converging roles of caspases in inflammasome activation, cell death and innate immunity. Nature Reviews. Immunology. 2016; 16: 7–21.
[36] Tschoe C, Bushnell CD, Duncan PW, Alexander-Miller MA, Wolfe SQ. Neuroinflammation after Intracerebral Hemorrhage and Potential Therapeutic Targets. Journal of Stroke. 2020; 22: 29–46.
[37] Li Z, Khan S, Liu Y, Wei R, Yong VW, Xue M. Therapeutic strategies for intracerebral hemorrhage. Frontiers in Neurology. 2022; 13: 1032343.
[38] Yoshida H, Yanai H, Namiki Y, Fukatsu-Sasaki K, Furutani N, Tada N. Neuroprotective effects of edaravone: a novel free radical scavenger in cerebrovascular injury. CNS Drug Reviews. 2006; 12: 9–20.
[39] Zhang Y, Khan S, Liu Y, Wu G, Yong VW, Xue M. Oxidative Stress Following Intracerebral Hemorrhage: From Molecular Mechanisms to Therapeutic Targets. Frontiers in Immunology. 2022; 13: 847246.
[40] Yang G, Fan X, Mazhar M, Guo W, Zou Y, Dechsupa N, *et al*. Neuroinflammation of microglia polarization in intracerebral hemorrhage and its potential targets for intervention. Frontiers in Molecular Neuroscience. 2022; 15: 1013706.
[41] Nakamura T, Kuroda Y, Yamashita S, Zhang X, Miyamoto O, Tamiya T, et al. Edaravone attenuates brain edema and neurologic deficits in a rat model of acute intracerebral hemorrhage. Stroke. 2008; 39:463-469.
[42] Qin M, Feng L, Yang C, Wei D, Li T, Jiang P, *et al*. Edaravone use in acute intracerebral hemorrhage: A systematic review and meta-analysis of randomized controlled trials. Frontiers in Pharmacology. 2022; 13: 935198.
[43] Li Y, Huang H, Liu B, Zhang Y, Pan X, Yu XY, *et al*. Inflammasomes as therapeutic targets in human diseases. Signal Transduction and Targeted Therapy. 2021; 6: 247.
[44] Sultana S, Viet TD, Amin T, Kazi E, Micolucci L, Mollah AKMM, *et al*. Exploring Inflammasome Complex as a Therapeutic Approach in Inflammatory Diseases. Future Pharmacology. 2023; 3: 789–818.
[45] Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cellular & Molecular Immunology. 2021; 18: 1141–1160.
[46] Duan Y, Wang J, Cai J, Kelley N, He Y. The leucine-rich repeat (LRR) domain of NLRP3 is required for NLRP3 inflammasome activation in macrophages. The Journal of Biological Chemistry. 2022; 298: 102717.
[47] Akbal A, Dernst A, Lovotti M, Mangan MSJ, McManus RM, Latz E. How location and cellular signaling combine to activate the NLRP3 inflammasome. Cellular & Molecular Immunology. 2022; 19: 1201–1214.
[48] Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. Cellular & Molecular Immunology. 2021; 18: 2114–2127.
[49] Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. Signal Transduction and Targeted Therapy. 2020; 5: 209.
[50] Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. Cell Death & Disease. 2019; 10: 128.
[51] Lamkanfi M, Dixit VM. Inflammasomes and their roles in health and disease. Annual Review of Cell and Developmental Biology. 2012; 28: 137–161.
[52] Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, *et al*. Cutting edge: NF-kappaB activating pattern

recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. Journal of Immunology (Baltimore, Md.: 1950). 2009; 183: 787–791.
[53] Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annual Review of Immunology. 2009; 27: 519–550.
[54] Moretti J, Blander JM. Increasing complexity of NLRP3 inflammasome regulation. Journal of Leukocyte Biology. 2021; 109: 561–571.
[55] He Y, Hara H, Núñez G. Mechanism and Regulation of NLRP3 Inflammasome Activation. Trends in Biochemical Sciences. 2016; 41: 1012–1021.
[56] Que X, Zheng S, Song Q, Pei H, Zhang P. Fantastic voyage: The journey of NLRP3 inflammasome activation. Genes & Diseases. 2023; 11: 819–829.
[57] Ji X, Song Z, He J, Guo S, Chen Y, Wang H, *et al*. NIMA-related kinase 7 amplifies NLRP3 inflammasome pro-inflammatory signaling in microglia/macrophages and mice models of spinal cord injury. Experimental Cell Research. 2021; 398: 112418.
[58] Ohto U, Kamitsukasa Y, Ishida H, Zhang Z, Murakami K, Hirama C, *et al*. Structural basis for the oligomerization-mediated regulation of NLRP3 inflammasome activation. Proceedings of the National Academy of Sciences of the United States of America. 2022; 119: e2121353119.
[59] Hochheiser IV, Behrmann H, Hagelueken G, Rodríguez-Alcázar JF, Kopp A, Latz E, *et al*. Directionality of PYD filament growth determined by the transition of NLRP3 nucleation seeds to ASC elongation. Science Advances. 2022; 8: eabn7583.
[60] Makoni NJ, Nichols MR. The intricate biophysical puzzle of caspase-1 activation. Archives of Biochemistry and Biophysics. 2021; 699: 108753.
[61] Newton K, Dixit VM. Signaling in innate immunity and inflammation. Cold Spring Harbor Perspectives in Biology. 2012; 4: a006049.
[62] Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nature Immunology. 2009; 10: 241–247.
[63] He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, *et al*. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Research. 2015; 25: 1285–1298.
[64] Dai Z, Liu WC, Chen XY, Wang X, Li JL, Zhang X. Gasdermin D-mediated pyroptosis: mechanisms, diseases, and inhibitors. Frontiers in Immunology. 2023; 14: 1178662.
[65] Tezcan G, Martynova EV, Gilazieva ZE, McIntyre A, Rizvanov AA, Khaiboullina SF. MicroRNA Post-transcriptional Regulation of the NLRP3 Inflammasome in Immunopathologies. Frontiers in Pharmacology. 2019; 10: 451.
[66] Swanson KV, Deng M, Ting JPY. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nature Reviews. Immunology. 2019; 19: 477–489.
[67] Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nature Reviews. Immunology. 2016; 16: 407–420.
[68] Paget C, Doz-Deblauwe E, Winter N, Briard B. Specific NLRP3 Inflammasome Assembling and Regulation in Neutrophils: Relevance in Inflammatory and Infectious Diseases. Cells. 2022; 11: 1188.
[69] Honda TSB, Ku J, Anders HJ. Cell type-specific roles of NLRP3, inflammasome-dependent and -independent, in host defense, sterile necroinflammation, tissue repair, and fibrosis. Frontiers in Immunology. 2023; 14: 1214289.
[70] Fusco R, Siracusa R, Genovese T, Cuzzocrea S, Di Paola R. Focus on the Role of NLRP3 Inflammasome in Diseases. International Journal of Molecular Sciences. 2020; 21: 4223.
[71] Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, *et al*. Non-canonical inflammasome activation targets caspase-11. Nature. 2011; 479: 117–121.
[72] Gurung P, Anand PK, Malireddi RKS, Vande Walle L, Van Opdenbosch N, Dillon CP, *et al*. FADD and caspase-8 mediate priming and activation of the canonical and noncanonical Nlrp3 inflammasomes. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 1835–1846.
[73] Yi YS. Caspase-11 non-canonical inflammasome: a critical sensor of intracellular lipopolysaccharide in macrophage-mediated inflammatory responses. Immunology. 2017; 152: 207–217.
[74] Kim YD. Systemic autoinflammatory disorders: autoinflammatory and autoimmune disorders. Clinical and Experimental Pediatrics. 2023; 66: 439–440.
[75] Prakash AV, Park IH, Park JW, Bae JP, Lee GS, Kang TJ. NLRP3 Inflammasome as Therapeutic Targets in Inflammatory Diseases. Biomolecules & Therapeutics. 2023; 31: 395–401.
[76] Xia J, Jiang S, Dong S, Liao Y, Zhou Y. The Role of Post-Translational Modifications in Regulation of NLRP3 Inflammasome Activation. International Journal of Molecular Sciences. 2023; 24: 6126.
[77] Akther M, Haque ME, Park J, Kang TB, Lee KH. NLRP3 Ubiquitination-A New Approach to Target NLRP3 Inflammasome Activation. International Journal of Molecular Sciences. 2021; 22: 8780.
[78] Seok JK, Kang HC, Cho YY, Lee HS, Lee JY. Regulation of the NLRP3 Inflammasome by Post-Translational Modifications and Small Molecules. Frontiers in Immunology. 2021; 11: 618231.
[79] Song N, Li T. Regulation of NLRP3 Inflammasome by Phosphorylation. Frontiers in Immunology. 2018; 9: 2305.
[80] Zhang Z, Meszaros G, He WT, Xu Y, de Fatima Magliarelli H, Mailly L, *et al*. Protein kinase D at the Golgi controls NLRP3 inflammasome activation. The Journal of Experimental Medicine. 2017; 214: 2671–2693.
[81] McKee CM, Fischer FA, Bezbradica JS, Coll RC. PHOrming the inflammasome: phosphorylation is a critical switch in inflammasome signalling. Biochemical Society Transactions. 2021; 49: 2495–2507.
[82] Song N, Liu ZS, Xue W, Bai ZF, Wang QY, Dai J, *et al*. NLRP3 Phosphorylation Is an Essential Priming Event for Inflammasome Activation. Molecular Cell. 2017; 68: 185–197.e6.
[83] Spalinger MR, Kasper S, Gottier C, Lang S, Atrott K, Vavricka SR, *et al*. NLRP3 tyrosine phosphorylation is controlled by protein tyrosine phosphatase PTPN22. The Journal of Clinical Investigation. 2016; 126: 1783–1800.
[84] Song H, Zhao C, Yu Z, Li Q, Yan R, Qin Y, *et al*. UAF1 deubiquitinase complexes facilitate NLRP3 inflammasome activation by promoting NLRP3 expression. Nature Communications. 2020; 11: 6042.
[85] Song H, Liu B, Huai W, Yu Z, Wang W, Zhao J, *et al*. The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation by promoting proteasomal degradation of NLRP3. Nature Communications. 2016; 7: 13727.
[86] Tang T, Li P, Zhou X, Wang R, Fan X, Yang M, *et al*. The E3 Ubiquitin Ligase TRIM65 Negatively Regulates Inflammasome Activation Through Promoting Ubiquitination of NLRP3. Frontiers in Immunology. 2021; 12: 741839.
[87] Qin Y, Li Q, Liang W, Yan R, Tong L, Jia M, *et al*. TRIM28 SUMOylates and stabilizes NLRP3 to facilitate inflammasome activation. Nature Communications. 2021; 12: 4794.
[88] Barry R, John SW, Liccardi G, Tenev T, Jaco I, Chen CH, *et al*. SUMO-mediated regulation of NLRP3 modulates inflammasome activity. Nature Communications. 2018; 9: 3001.
[89] Mao K, Chen S, Chen M, Ma Y, Wang Y, Huang B, *et al*. Nitric oxide suppresses NLRP3 inflammasome activation and protects against LPS-induced septic shock. Cell Research. 2013; 23: 201–212.
[90] Chiu LY, Huang DY, Lin WW. PARP-1 regulates inflammasome activity by poly-ADP-ribosylation of NLRP3 and interac-

tion with TXNIP in primary macrophages. Cellular and Molecular Life Sciences: CMLS. 2022; 79: 108.
[91] Dancy BM, Cole PA. Protein lysine acetylation by p300/CBP. Chemical Reviews. 2015; 115: 2419–2452.
[92] Yu T, Hou D, Zhao J, Lu X, Greentree WK, Zhao Q, *et al*. NLRP3 Cys126 palmitoylation by ZDHHC7 promotes inflammasome activation. Cell Reports. 2024; 43: 114070.
[93] Kattah MG, Malynn BA, Ma A. Ubiquitin-Modifying Enzymes and Regulation of the Inflammasome. Journal of Molecular Biology. 2017; 429: 3471–3485.
[94] Li J, Chai QY, Liu CH. The ubiquitin system: a critical regulator of innate immunity and pathogen-host interactions. Cellular & Molecular Immunology. 2016; 13: 560–576.
[95] Yu Q, Shi H, Ding Z, Wang Z, Yao H, Lin R. The E3 ubiquitin ligase TRIM31 attenuates NLRP3 inflammasome activation in Helicobacter pylori-associated gastritis by regulating ROS and autophagy. Cell Communication and Signaling: CCS. 2023; 21: 1.
[96] Lin H, Li S, Shu HB. The Membrane-Associated MARCH E3 Ligase Family: Emerging Roles in Immune Regulation. Frontiers in Immunology. 2019; 10: 1751.
[97] McKee CM, Coll RC. NLRP3 inflammasome priming: A riddle wrapped in a mystery inside an enigma. Journal of Leukocyte Biology. 2020; 108: 937–952.
[98] Cai B, Zhao J, Zhang Y, Liu Y, Ma C, Yi F, *et al*. USP5 attenuates NLRP3 inflammasome activation by promoting autophagic degradation of NLRP3. Autophagy. 2022; 18: 990–1004.
[99] Yan Y, Jiang W, Liu L, Wang X, Ding C, Tian Z, *et al*. Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome. Cell. 2015; 160: 62–73.
[100] Tang J, Tu S, Lin G, Guo H, Yan C, Liu Q, *et al*. Sequential ubiquitination of NLRP3 by RNF125 and Cbl-b limits inflammasome activation and endotoxemia. The Journal of Experimental Medicine. 2020; 217: e20182091.
[101] Lin HC, Chen YJ, Wei YH, Chuang YT, Hsieh SH, Hsieh JY, *et al*. Cbl Negatively Regulates NLRP3 Inflammasome Activation through GLUT1-Dependent Glycolysis Inhibition. International Journal of Molecular Sciences. 2020; 21: 5104.
[102] Chen BB, Glasser JR, Coon TA, Mallampalli RK. Skp-cullin-F box E3 ligase component FBXL2 ubiquitinates Aurora B to inhibit tumorigenesis. Cell Death & Disease. 2013; 4: e759.
[103] Han S, Lear TB, Jerome JA, Rajbhandari S, Snavely CA, Gulick DL, *et al*. Lipopolysaccharide Primes the NALP3 Inflammasome by Inhibiting Its Ubiquitination and Degradation Mediated by the SCFFBXL2 E3 Ligase. The Journal of Biological Chemistry. 2015; 290: 18124–18133.
[104] Grice GL, Nathan JA. The recognition of ubiquitinated proteins by the proteasome. Cellular and Molecular Life Sciences: CMLS. 2016; 73: 3497–3506.
[105] Lopez-Castejon G. Control of the inflammasome by the ubiquitin system. The FEBS Journal. 2020; 287: 11–26.
[106] Geng S, Peng W, Wang X, Hu X, Liang H, Hou J, *et al*. ARIH2 regulates the proliferation, DNA damage and chemosensitivity of gastric cancer cells by reducing the stability of p21 via ubiquitination. Cell Death & Disease. 2022; 13: 564.
[107] Spratt DE, Walden H, Shaw GS. RBR E3 ubiquitin ligases: new structures, new insights, new questions. The Biochemical Journal. 2014; 458: 421-437.
[108] Kawashima A, Karasawa T, Tago K, Kimura H, Kamata R, Usui-Kawanishi F, *et al*. ARIH2 Ubiquitinates NLRP3 and Negatively Regulates NLRP3 Inflammasome Activation in Macrophages. Journal of Immunology (Baltimore, Md.: 1950). 2017; 199: 3614–3622.
[109] Smit JJ, Sixma TK. RBR E3-ligases at work. EMBO Reports. 2014; 15: 142–154.
[110] Wan P, Zhang Q, Liu W, Jia Y, Ai S, Wang T, *et al*. Cullin1 binds and promotes NLRP3 ubiquitination to repress systematic inflammasome activation. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2019; 33: 5793–5807.
[111] Xie CM, Wei W, Sun Y. Role of SKP1-CUL1-F-box-protein (SCF) E3 ubiquitin ligases in skin cancer. Journal of Genetics and Genomics = Yi Chuan Xue Bao. 2013; 40: 97–106.
[112] Liang Z, Damianou A, Di Daniel E, Kessler BM. Inflammasome activation controlled by the interplay between post-translational modifications: emerging drug target opportunities. Cell Communication and Signaling: CCS. 2021; 19: 23.
[113] Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. Nature Reviews. Immunology. 2013; 13: 397–411.
[114] Humphries F, Bergin R, Jackson R, Delagic N, Wang B, Yang S, *et al*. The E3 ubiquitin ligase Pellino2 mediates priming of the NLRP3 inflammasome. Nature Communications. 2018; 9: 1560.
[115] Zhang E, Li X. The Emerging Roles of Pellino Family in Pattern Recognition Receptor Signaling. Frontiers in Immunology. 2022; 13: 728794.
[116] O'Keefe ME, Dubyak GR, Abbott DW. Post-translational control of NLRP3 inflammasome signaling. The Journal of Biological Chemistry. 2024; 300: 107386.
[117] Oleszycka E, Rodgers AM, Xu L, Moynagh PN. Dendritic Cell-Specific Role for Pellino2 as a Mediator of TLR9 Signaling Pathway. Journal of Immunology (Baltimore, Md.: 1950). 2021; 207: 2325–2336.
[118] Walsh MC, Lee J, Choi Y. Tumor necrosis factor receptor-associated factor 6 (TRAF6) regulation of development, function, and homeostasis of the immune system. Immunological Reviews. 2015; 266: 72–92.
[119] Chen M, Yu S, Gao Y, Li J, Wang X, Wei B, *et al*. TRAF6-TAK1-IKKβ pathway mediates TLR2 agonists activating "one-step" NLRP3 inflammasome in human monocytes. Cytokine. 2023; 169: 156302.
[120] Kim SK. The Mechanism of the NLRP3 Inflammasome Activation and Pathogenic Implication in the Pathogenesis of Gout. Journal of Rheumatic Diseases. 2022; 29: 140–153.
[121] Yan W, Sun W, Fan J, Wang H, Han S, Li J, *et al*. Sirt1-ROS-TRAF6 Signaling-Induced Pyroptosis Contributes to Early Injury in Ischemic Mice. Neuroscience Bulletin. 2020; 36: 845–859.
[122] Xing Y, Yao X, Li H, Xue G, Guo Q, Yang G, *et al*. Cutting Edge: TRAF6 Mediates TLR/IL-1R Signaling-Induced Nontranscriptional Priming of the NLRP3 Inflammasome. Journal of Immunology (Baltimore, Md.: 1950). 2017; 199: 1561–1566.
[123] Chen Y, Ye X, Escames G, Lei W, Zhang X, Li M, *et al*. The NLRP3 inflammasome: contributions to inflammation-related diseases. Cellular & Molecular Biology Letters. 2023; 28: 51.
[124] Wang J, Wu X, Jiang M, Tai G. Mechanism by which TRAF6 Participates in the Immune Regulation of Autoimmune Diseases and Cancer. BioMed Research International. 2020; 2020: 4607197.
[125] Kodi T, Sankhe R, Gopinathan A, Nandakumar K, Kishore A. New Insights on NLRP3 Inflammasome: Mechanisms of Activation, Inhibition, and Epigenetic Regulation. Journal of Neuroimmune Pharmacology: the Official Journal of the Society on NeuroImmune Pharmacology. 2024; 19: 7.
[126] Abbott DW, Yang Y, Hutti JE, Madhavarapu S, Kelliher MA, Cantley LC. Coordinated regulation of Toll-like receptor and NOD2 signaling by K63-linked polyubiquitin chains. Molecular and Cellular Biology. 2007; 27: 6012–6025.
[127] Cockram PE, Kist M, Prakash S, Chen SH, Wertz IE, Vucic D. Ubiquitination in the regulation of inflammatory cell death and cancer. Cell Death and Differentiation. 2021; 28: 591–605.
[128] Py BF, Kim MS, Vakifahmetoglu-Norberg H, Yuan J. Deubiquitination of NLRP3 by BRCC3 critically regulates inflamma-

some activity. Molecular Cell. 2013; 49: 331–338.
[129] Pan X, Wu S, Wei W, Chen Z, Wu Y, Gong K. Structural and Functional Basis of JAMM Deubiquitinating Enzymes in Disease. Biomolecules. 2022; 12: 910.
[130] Miskinyte S, Butler MG, Hervé D, Sarret C, Nicolino M, Petralia JD, *et al*. Loss of BRCC3 deubiquitinating enzyme leads to abnormal angiogenesis and is associated with syndromic moyamoya. American Journal of Human Genetics. 2011; 88: 718–728.
[131] Yang C, Liu J, Zhao S, Shang Q, Ren F, Feng K, *et al*. Infiltrating myeloid cell diversity determines oncological characteristics and clinical outcomes in breast cancer. Breast Cancer Research: BCR. 2023; 25: 63.
[132] Bhattacharya S, Chakraborty D, Basu M, Ghosh MK. Emerging insights into HAUSP (USP7) in physiology, cancer and other diseases. Signal Transduction and Targeted Therapy. 2018; 3: 17.
[133] Qi SM, Cheng G, Cheng XD, Xu Z, Xu B, Zhang WD, *et al*. Targeting USP7-Mediated Deubiquitination of MDM2/MDMX-p53 Pathway for Cancer Therapy: Are We There Yet? Frontiers in Cell and Developmental Biology. 2020; 8: 233.
[134] Parsons JL, Dianova II, Khoronenkova SV, Edelmann MJ, Kessler BM, Dianov GL. USP47 is a deubiquitylating enzyme that regulates base excision repair by controlling steady-state levels of DNA polymerase β. Molecular Cell. 2011; 41: 609–615.
[135] Palazón-Riquelme P, Worboys JD, Green J, Valera A, Martín-Sánchez F, Pellegrini C, *et al*. USP7 and USP47 deubiquitinases regulate NLRP3 inflammasome activation. EMBO Reports. 2018; 19: e44766.
[136] Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1β secretion. Cytokine & Growth Factor Reviews. 2011; 22: 189–195.
[137] Liang Z, Damianou A, Vendrell I, Jenkins E, Lassen FH, Washer SJ, *et al*. Proximity proteomics reveals UCH-L1 as an essential regulator of NLRP3-mediated IL-1β production in human macrophages and microglia. Cell Reports. 2024; 43: 114152.
[138] Moltrasio C, Romagnuolo M, Marzano AV. NLRP3 inflammasome and NLRP3-related autoinflammatory diseases: From cryopyrin function to targeted therapies. Frontiers in Immunology. 2022; 13: 1007705.
[139] Guo NJ, Wang B, Zhang Y, Kang HQ, Nie HQ, Feng MK, *et al*. USP7 as an emerging therapeutic target: A key regulator of protein homeostasis. International Journal of Biological Macromolecules. 2024; 263: 130309.
[140] Pan K, Fu J, Xu W. Role of Ubiquitin-Specific Peptidase 47 in Cancers and Other Diseases. Frontiers in Cell and Developmental Biology. 2021; 9: 726632.
[141] Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, *et al*. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017; 9: 7204–7218.
[142] Xu T, Guo Y, Qi X. Ubiquitination-Mediated Inflammasome Activation during Bacterial Infection. International Journal of Molecular Sciences. 2019; 20: 2110.
[143] Martens A, van Loo G. A20 at the Crossroads of Cell Death, Inflammation, and Autoimmunity. Cold Spring Harbor Perspectives in Biology. 2020; 12: a036418.
[144] Bai W, Huo S, Li J, Shao J. Advances in the Study of the Ubiquitin-Editing Enzyme A20. Frontiers in Pharmacology. 2022; 13: 845262.
[145] Wu Y, He X, Huang N, Yu J, Shao B. A20: a master regulator of arthritis. Arthritis Research & Therapy. 2020; 22: 220.
[146] Duong BH, Onizawa M, Oses-Prieto JA, Advincula R, Burlingame A, Malynn BA, *et al*. A20 restricts ubiquitination of pro-interleukin-1β protein complexes and suppresses NLRP3 inflammasome activity. Immunity. 2015; 42: 55–67.
[147] Yu J, Li H, Wu Y, Luo M, Chen S, Shen G, *et al*. Inhibition of NLRP3 inflammasome activation by A20 through modulation of NEK7. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2316551121.
[148] Rohwedder I, Wackerbarth LM, Heinig K, Ballweg A, Altstätter J, Ripphahn M, *et al*. A20 and the noncanonical NF-κB pathway are key regulators of neutrophil recruitment during fetal ontogeny. JCI Insight. 2023; 8: e155968.
[149] Catrysse L, Vereecke L, Beyaert R, van Loo G. A20 in inflammation and autoimmunity. Trends in Immunology. 2014; 35: 22–31.
[150] Mouton-Liger F, Rosazza T, Sepulveda-Diaz J, Ieang A, Hassoun SM, Claire E, *et al*. Parkin deficiency modulates NLRP3 inflammasome activation by attenuating an A20-dependent negative feedback loop. Glia. 2018; 66: 1736–1751.
[151] Yin H, Liu N, Sigdel KR, Duan L. Role of NLRP3 Inflammasome in Rheumatoid Arthritis. Frontiers in Immunology. 2022; 13: 931690.
[152] Filardy AA, He J, Bennink J, Yewdell J, Kelsall BL. Post-transcriptional control of NLRP3 inflammasome activation in colonic macrophages. Mucosal Immunology. 2016; 9: 850–858.
[153] Park YJ, Dodantenna N, Kim Y, Kim TH, Lee HS, Yoo YS, *et al*. MARCH5-dependent NLRP3 ubiquitination is required for mitochondrial NLRP3-NEK7 complex formation and NLRP3 inflammasome activation. The EMBO Journal. 2023; 42: e113481.
[154] Di Q, Zhao X, Tang H, Li X, Xiao Y, Wu H, *et al*. USP22 suppresses the NLRP3 inflammasome by degrading NLRP3 via ATG5-dependent autophagy. Autophagy. 2023; 19: 873–885.
[155] Valerdi KM, Hage A, van Tol S, Rajsbaum R, Giraldo MI. The Role of the Host Ubiquitin System in Promoting Replication of Emergent Viruses. Viruses. 2021; 13: 369.
[156] Berglund J, Gjondrekaj R, Verney E, Maupin-Furlow JA, Edelmann MJ. Modification of the host ubiquitome by bacterial enzymes. Microbiological Research. 2020; 235: 126429.
[157] Rastogi S, Ellinwood S, Augenstreich J, Mayer-Barber KD, Briken V. Mycobacterium tuberculosis inhibits the NLRP3 inflammasome activation via its phosphokinase PknF. PLoS Pathogens. 2021; 17: e1009712.
[158] Master SS, Rampini SK, Davis AS, Keller C, Ehlers S, Springer B, *et al*. Mycobacterium tuberculosis prevents inflammasome activation. Cell Host & Microbe. 2008; 3: 224–232.
[159] Zhou H, Monack DM, Kayagaki N, Wertz I, Yin J, Wolf B, *et al*. Yersinia virulence factor YopJ acts as a deubiquitinase to inhibit NF-kappa B activation. The Journal of Experimental Medicine. 2005; 202: 1327–1332.
[160] LaRock CN, Cookson BT. The Yersinia virulence effector YopM binds caspase-1 to arrest inflammasome assembly and processing. Cell Host & Microbe. 2012; 12: 799–805.
[161] Suzuki S, Mimuro H, Kim M, Ogawa M, Ashida H, Toyotome T, *et al*. Shigella IpaH7.8 E3 ubiquitin ligase targets glomulin and activates inflammasomes to demolish macrophages. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111: E4254–E4263.
[162] Kim S, Bauernfeind F, Ablasser A, Hartmann G, Fitzgerald KA, Latz E, *et al*. Listeria monocytogenes is sensed by the NLRP3 and AIM2 inflammasome. European Journal of Immunology. 2010; 40: 1545–1551.
[163] Yang J, Wang Y, Hou Y, Sun M, Xia T, Wu X. Evasion of host defense by *Brucella*. Cell Insight. 2023; 3: 100143.
[164] Wood SJ, Goldufsky JW, Seu MY, Dorafshar AH, Shafikhani SH. *Pseudomonas aeruginosa* Cytotoxins: Mechanisms of Cytotoxicity and Impact on Inflammatory Responses. Cells. 2023; 12: 195.
[165] Qin S, Xiao W, Zhou C, Pu Q, Deng X, Lan L, *et al*. Pseudomonas aeruginosa: pathogenesis, virulence factors, antibiotic resistance, interaction with host, technology advances and

emerging therapeutics. Signal Transduction and Targeted Therapy. 2022; 7: 199.

[166] Kubori T, Hyakutake A, Nagai H. Legionella translocates an E3 ubiquitin ligase that has multiple U-boxes with distinct functions. Molecular Microbiology. 2008; 67: 1307–1319.

[167] Naseer N, Egan MS, Reyes Ruiz VM, Scott WP, Hunter EN, Demissie T, *et al*. Human NAIP/NLRC4 and NLRP3 inflammasomes detect Salmonella type III secretion system activities to restrict intracellular bacterial replication. PLoS Pathogens. 2022; 18: e1009718.

[168] Atianand MK, Duffy EB, Shah A, Kar S, Malik M, Harton JA. Francisella tularensis reveals a disparity between human and mouse NLRP3 inflammasome activation. The Journal of Biological Chemistry. 2011; 286: 39033–39042.

[169] Sahni A, Fang R, Sahni SK, Walker DH. Pathogenesis of Rickettsial Diseases: Pathogenic and Immune Mechanisms of an Endotheliotropic Infection. Annual Review of Pathology. 2019; 14: 127–152.

[170] Carey KL, Newton HJ, Lührmann A, Roy CR. The Coxiella burnetii Dot/Icm system delivers a unique repertoire of type IV effectors into host cells and is required for intracellular replication. PLoS Pathogens. 2011; 7: e1002056.

[171] Valderrama JA, Nizet V. Group A Streptococcus encounters with host macrophages. Future Microbiology. 2018; 13: 119–134.

[172] Hancz D, Westerlund E, Valfridsson C, Aemero GM, Bastiat-Sempe B, Orning P, *et al*. Streptolysin O Induces the Ubiquitination and Degradation of Pro-IL-1β. Journal of Innate Immunity. 2019; 11: 457–468.

[173] Chopra A, Bhat SG, Sivaraman K. Porphyromonas gingivalis adopts intricate and unique molecular mechanisms to survive and persist within the host: a critical update. Journal of Oral Microbiology. 2020; 12: 1801090.

[174] Okano T, Ashida H, Suzuki S, Shoji M, Nakayama K, Suzuki T. Porphyromonas gingivalis triggers NLRP3-mediated inflammasome activation in macrophages in a bacterial gingipains-independent manner. European Journal of Immunology. 2018; 48: 1965–1974.

[175] Duncan JA, Gao X, Huang MTH, O'Connor BP, Thomas CE, Willingham SB, *et al*. Neisseria gonorrhoeae activates the proteinase cathepsin B to mediate the signaling activities of the NLRP3 and ASC-containing inflammasome. Journal of Immunology (Baltimore, Md.: 1950). 2009; 182: 6460–6469.

[176] Helble JD, McCarthy JE, Hu LT. Interactions between Borrelia burgdorferi and its hosts across the enzootic cycle. Parasite Immunology. 2021; 43: e12816.

[177] Shaw DK, McClure EE, Wang X, Pedra JHF. Deviant Behavior: Tick-Borne Pathogens and Inflammasome Signaling. Veterinary Sciences. 2016; 3: 27.

[178] Wong MT, Chen SSL. Emerging roles of interferon-stimulated genes in the innate immune response to hepatitis C virus infection. Cellular & Molecular Immunology. 2016; 13: 11–35.

[179] Aguirre S, Luthra P, Sanchez-Aparicio MT, Maestre AM, Patel J, Lamothe F, *et al*. Dengue virus NS2B protein targets cGAS for degradation and prevents mitochondrial DNA sensing during infection. Nature Microbiology. 2017; 2: 17037.

[180] Li S, Hong X, Wei Z, Xie M, Li W, Liu G, *et al*. Ubiquitination of the HPV Oncoprotein E6 Is Critical for E6/E6AP-Mediated p53 Degradation. Frontiers in Microbiology. 2019; 10: 2483.

[181] Saito S, Murata T, Kanda T, Isomura H, Narita Y, Sugimoto A, *et al*. Epstein-Barr virus deubiquitinase downregulates TRAF6-mediated NF-κB signaling during productive replication. Journal of Virology. 2013; 87: 4060–4070.

[182] Inn KS, Lee SH, Rathbun JY, Wong LY, Toth Z, Machida K, *et al*. Inhibition of RIG-I-mediated signaling by Kaposi's sarcoma-associated herpesvirus-encoded deubiquitinase ORF64. Journal of Virology. 2011; 85: 10899–10904.

[183] Xiao H, Li J, Yang X, Li Z, Wang Y, Rui Y, *et al*. Ectopic Expression of TRIM25 Restores RIG-I Expression and IFN Production Reduced by Multiple Enteroviruses $3C^{pro}$. Virologica Sinica. 2021; 36: 1363–1374.

[184] DeMeritt IB, Podduturi JP, Tilley AM, Nogalski MT, Yurochko AD. Prolonged activation of NF-kappaB by human cytomegalovirus promotes efficient viral replication and late gene expression. Virology. 2006; 346: 15–31.

[185] Lanfranca MP, Mostafa HH, Davido DJ. HSV-1 ICP0: An E3 Ubiquitin Ligase That Counteracts Host Intrinsic and Innate Immunity. Cells. 2014; 3: 438–454.

[186] Komune N, Ichinohe T, Ito M, Yanagi Y. Measles virus V protein inhibits NLRP3 inflammasome-mediated interleukin-1β secretion. Journal of Virology. 2011; 85: 13019–13026.

[187] Zhao C, Zhao W. NLRP3 Inflammasome-A Key Player in Antiviral Responses. Frontiers in Immunology. 2020; 11: 211.

[188] Tchesnokov EP, Bailey-Elkin BA, Mark BL, Götte M. Independent inhibition of the polymerase and deubiquitinase activities of the Crimean-Congo Hemorrhagic Fever Virus full-length L-protein. PLoS Neglected Tropical Diseases. 2020; 14: e0008283.

[189] Ta A, Vanaja SK. Inflammasome activation and evasion by bacterial pathogens. Current Opinion in Immunology. 2021; 68: 125–133.

[190] Kim JJ, Jo EK. NLRP3 inflammasome and host protection against bacterial infection. Journal of Korean Medical Science. 2013; 28: 1415–1423.

[191] Shariq M, Quadir N, Alam A, Zarin S, Sheikh JA, Sharma N, *et al*. The exploitation of host autophagy and ubiquitin machinery by *Mycobacterium tuberculosis* in shaping immune responses and host defense during infection. Autophagy. 2023; 19: 3–23.

[192] Wang J, Ge P, Lei Z, Lu Z, Qiang L, Chai Q, *et al*. Mycobacterium tuberculosis protein kinase G acts as an unusual ubiquitinating enzyme to impair host immunity. EMBO Reports. 2021; 22: e52175.

[193] Ferraris DM, Sbardella D, Petrera A, Marini S, Amstutz B, Coletta M, *et al*. Crystal structure of Mycobacterium tuberculosis zinc-dependent metalloprotease-1 (Zmp1), a metalloprotease involved in pathogenicity. The Journal of Biological Chemistry. 2011; 286: 32475–32482.

[194] Cornelis GR. Yersinia type III secretion: send in the effectors. The Journal of Cell Biology. 2002; 158: 401–408.

[195] Zheng Y, Lilo S, Brodsky IE, Zhang Y, Medzhitov R, Marcu KB, *et al*. A Yersinia effector with enhanced inhibitory activity on the NF-κB pathway activates the NLRP3/ASC/caspase-1 inflammasome in macrophages. PLoS Pathogens. 2011; 7: e1002026.

[196] Wei C, Wang Y, Du Z, Guan K, Cao Y, Yang H, *et al*. The Yersinia Type III secretion effector YopM Is an E3 ubiquitin ligase that induced necrotic cell death by targeting NLRP3. Cell Death & Disease. 2016; 7: e2519.

[197] Wang C, Shivcharan S, Tian T, Wright S, Ma D, Chang J, *et al*. Structural basis for GSDMB pore formation and its targeting by IpaH7.8. Nature. 2023; 616: 590–597.

[198] Seveau S, Pizarro-Cerda J, Cossart P. Molecular mechanisms exploited by Listeria monocytogenes during host cell invasion. Microbes and Infection. 2007; 9: 1167–1175.

[199] Seveau S. Multifaceted activity of listeriolysin O, the cholesterol-dependent cytolysin of Listeria monocytogenes. Sub-cellular Biochemistry. 2014; 80: 161–195.

[200] Theisen E, Sauer JD. Listeria monocytogenes and the Inflammasome: From Cytosolic Bacteriolysis to Tumor Immunotherapy. Current Topics in Microbiology and Immunology. 2016; 397: 133–160.

[201] Nguyen BN, Peterson BN, Portnoy DA. Listeriolysin O: A phagosome-specific cytolysin revisited. Cellular Microbiology. 2019; 21: e12988.

[202] Gouin E, Adib-Conquy M, Balestrino D, Nahori MA, Villiers V, Colland F, *et al*. The Listeria monocytogenes InlC protein interferes with innate immune responses by targeting the I(127)B kinase subunit IKKalpha. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 17333–17338.
[203] Le Negrate G, Krieg A, Faustin B, Loeffler M, Godzik A, Krajewski S, *et al*. ChlaDub1 of Chlamydia trachomatis suppresses NF-kappaB activation and inhibits IkappaBalpha ubiquitination and degradation. Cellular Microbiology. 2008; 10: 1879–1892.
[204] Radhakrishnan GK, Yu Q, Harms JS, Splitter GA. Brucella TIR Domain-containing Protein Mimics Properties of the Toll-like Receptor Adaptor Protein TIRAP. The Journal of Biological Chemistry. 2009; 284: 9892–9898.
[205] Luo J, Wang L, Song L, Luo ZQ. Exploitation of the Host Ubiquitin System: Means by *Legionella pneumophila*. Frontiers in Microbiology. 2021; 12: 790442.
[206] Pillay TD, Hettiarachchi SU, Gan J, Diaz-Del-Olmo I, Yu XJ, Muench JH, *et al*. Speaking the host language: how *Salmonella* effector proteins manipulate the host. Microbiology (Reading, England). 2023; 169: 001342.
[207] Suresh RV, Bradley EW, Higgs M, Russo VC, Alqahtani M, Huang W, *et al*. Nlrp3 Increases the Host's Susceptibility to Tularemia. Frontiers in Microbiology. 2021; 12: 725572.
[208] Voss OH, Rahman MS. Rickettsia-host interaction: strategies of intracytosolic host colonization. Pathogens and Disease. 2021; 79: ftab015.
[209] Dragan AL, Voth DE. Coxiella burnetii: international pathogen of mystery. Microbes and Infection. 2020; 22: 100–110.
[210] Chiang-Ni C, Chiang CY, Chen YW, Shi YA, Chao YT, Wang S, *et al*. RopB-regulated SpeB cysteine protease degrades extracellular vesicles-associated streptolysin O and bacterial proteins from group A *Streptococcus*. Virulence. 2023; 14: 2249784.
[211] Walker E, van Niekerk S, Hanning K, Kelton W, Hicks J. Mechanisms of host manipulation by *Neisseria gonorrhoeae*. Frontiers in Microbiology. 2023; 14: 1119834.
[212] Kenedy MR, Lenhart TR, Akins DR. The role of Borrelia burgdorferi outer surface proteins. FEMS Immunology and Medical Microbiology. 2012; 66: 1–19.
[213] Shi W, Jin M, Chen H, Wu Z, Yuan L, Liang S, *et al*. Inflammasome activation by viral infection: mechanisms of activation and regulation. Frontiers in Microbiology. 2023; 14: 1247377.
[214] Gack MU, Albrecht RA, Urano T, Inn KS, Huang IC, Carnero E, *et al*. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. Cell Host & Microbe. 2009; 5: 439–449.
[215] Li XD, Sun L, Seth RB, Pineda G, Chen ZJ. Hepatitis C virus protease NS3/4A cleaves mitochondrial antiviral signaling protein off the mitochondria to evade innate immunity. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102: 17717–17722.
[216] Wang YQ, Zhao XY. Human Cytomegalovirus Primary Infection and Reactivation: Insights From Virion-Carried Molecules. Frontiers in Microbiology. 2020; 11: 1511.
[217] Zhang J, Wang K, Wang S, Zheng C. Herpes simplex virus 1 E3 ubiquitin ligase ICP0 protein inhibits tumor necrosis factor alpha-induced NF-κB activation by interacting with p65/RelA and p50/NF-κB1. Journal of Virology. 2013; 87: 12935–12948.
[218] Enchéry F, Dumont C, Iampietro M, Pelissier R, Aurine N, Bloyet LM, *et al*. Nipah virus W protein harnesses nuclear 14-3-3 to inhibit NF-κB-induced proinflammatory response. Communications Biology. 2021; 4: 1292.
[219] Zhu J, Chiang C, Gack MU. Viral evasion of the interferon response at a glance. Journal of Cell Science. 2023; 136: jcs260682.
[220] Alonaizan R. Molecular regulation of NLRP3 inflammasome activation during parasitic infection. Bioscience Reports. 2024; 44: BSR20231918.
[221] Chadha A, Chadee K. The NF-κB Pathway: Modulation by *Entamoeba histolytica* and Other Protozoan Parasites. Frontiers in Cellular and Infection Microbiology. 2021; 11: 748404.
[222] La Rosa F, Varotto-Boccazzi I, Saresella M, Marventano I, Cattaneo GM, Hernis A, *et al*. The non-pathogenic protozoon *Leishmania tarentolae* interferes with the activation of NLRP3 inflammasome in human cells: new perspectives in the control of inflammation. Frontiers in Immunology. 2024; 15: 1298275.
[223] Shio MT, Eisenbarth SC, Savaria M, Vinet AF, Bellemare MJ, Harder KW, *et al*. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. PLoS Pathogens. 2009; 5: e1000559.
[224] Henry B, Sibley LD, Rosenberg A. A Combination of Four Nuclear Targeted Effectors Protects Toxoplasma Against Interferon Gamma Driven Human Host Cell Death During Acute Infection. bioRxiv. 2023. (preprint)
[225] Guay-Vincent MM, Matte C, Berthiaume AM, Olivier M, Jaramillo M, Descoteaux A. Revisiting Leishmania GP63 host cell targets reveals a limited spectrum of substrates. PLoS Pathogens. 2022; 18: e1010640.
[226] Gupta AK, Das S, Kamran M, Ejazi SA, Ali N. The pathogenicity and virulence of Leishmania - interplay of virulence factors with host defenses. Virulence. 2022; 13: 903–935.
[227] Bougdour A, Durandau E, Brenier-Pinchart MP, Ortet P, Barakat M, Kieffer S, *et al*. Host cell subversion by Toxoplasma GRA16, an exported dense granule protein that targets the host cell nucleus and alters gene expression. Cell Host & Microbe. 2013; 13: 489–500.
[228] Sabou M, Doderer-Lang C, Leyer C, Konjic A, Kubina S, Lennon S, *et al*. Toxoplasma gondii ROP16 kinase silences the cyclin B1 gene promoter by hijacking host cell UHRF1-dependent epigenetic pathways. Cellular and Molecular Life Sciences: CMLS. 2020; 77: 2141–2156.
[229] Kim SG, Seo SH, Shin JH, Yang JP, Lee SH, Shin EH. Increase in the nuclear localization of PTEN by the Toxoplasma GRA16 protein and subsequent induction of p53-dependent apoptosis and anticancer effect. Journal of Cellular and Molecular Medicine. 2019; 23: 3234–3245.
[230] Hakimi MA, Bougdour A. Toxoplasma's ways of manipulating the host transcriptome via secreted effectors. Current Opinion in Microbiology. 2015; 26: 24–31.