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Functionalized nanomaterials targeting NLRP3 inflammasome driven immunomodulation: Friend or Foe

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The advancement in drug delivery systems in recent times has significantly enhanced therapeutic effects by enabling site-specific targeting through nanocarriers. These nanocarriers serve as invaluable tools for pharmacotherapeutic advancements against various disorders that enhance the effectiveness of encapsulated drugs by reducing their toxicity and increasing the efficacy of less potent drugs, thereby improving the therapeutic index. Inflammasomes, protein complexes located in the activated immune cell cytoplasm, regulate the activation of caspases involved in inflammation. However, aberrant activation of inflammasomes can result in uncontrolled tissue responses, contributing to the development of various diseases. Therefore, achieving a precise balance between inflammasome inhibition and activation is crucial for effectively treating inflammatory disorders through targeted functionalized nanocarriers. Despite the wealth of available data on the relevance of functionalized nanocarriers in inflammatory disorders, the nanotechnological potential to modulate inflammasomes has not been adequately explored. In this comprehensive review, we highlight the latest research on the modulation of the inflammasome cascade, both upregulating and downregulating its function, using nanocarriers in the context of inflammatory disorders. The utilization of nanocarriers as a therapeutic strategy holds immense potential for researchers aiming to effectively target and modulate inflammasomes in the treatment of inflammatory disorders, thus improving disease severity outcomes.

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1. Introduction

In the realm of pharmaceutical research, the application of nanotechnology has been substantially advanced in recent years, resulting in significant improvements. The use of nanomaterials for the prevention, diagnosis, treatment, examination and control of many diseases and disorders has made nanotechnology the most important Key Enabling Technology in the European Union. Drugs are delivered to the target cells by functionalised drug delivery nanocarriers that act specifically as nanomedicines through solubilization and active/passive diffusion by targeting any mechanistic pathway that would give a site specific therapeutic effect of the carrier that further would increase the efficacy of a drug that has less potency. Additionally, nanomaterial-based drug delivery carriers including exosomes, liposomes, metal-based nanoparticles, polymer-based nanoparticles, hydrogels, *etc.* are effective at treating inflammatory illnesses by taking advantage of various molecular signalling pathways.[1,2]

Amphiphilic copolymer chains exhibit self-assembly in aqueous environments, yielding polymeric nanoparticles. Utilizing distinct hydrophilic and hydrophobic blocks with varying structural, length, and charge attributes, a diverse array of polymeric nanoparticles has been synthesized. Liposomes, small amphipathic vesicles composed of phospholipids, exhibit varying properties influenced by lipid composition, size, surface charge, and production methods.[3] Exosomes, nanoscale extracellular vesicles, hold prominence in rapidly advancing research due to their role as messengers in diverse clinical disorders, pivotal for intercellular communication.[4] Metal nanoparticles garner substantial interest owing to optical traits like surface plasmon resonance (SPR), enabling optical field modulation for potential biomedical applications. Their diminutive size facilitates passage through biological membranes often impervious to larger macromolecules.[5] Amphiphilic monomers give rise to polymeric crosslinked networks, generating hydrogels with high water-holding capacity. Hydrogel formation involves supramolecular interactions like H-bonding, metal coordination, van der Waals forces, and electrostatic interactions, as well as polymeric bonding mechanisms.[6]

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In accordance with various studies reviewed by Nel *et al.* (2009), it is evident that the interaction between nanoparticles (NPs) and cells, as well as tissues *in vivo*, is influenced by the specific proteins to which they can bind. These interactions play a crucial role in determining the fate and behavior of NPs within the biological environment. Understanding the protein–NP interactions is essential for predicting the potential bio-distribution, cellular uptake, and overall biocompatibility of nanoparticles, which are crucial factors for their safe and effective use in various biomedical applications.[7]

The inflammasome pathway represents a pivotal signaling cascade involving cytosolic protein complexes known as inflammasomes. These complexes, originally identified by Martinon and colleagues in 2002, play a crucial role in orchestrating the activation of potent inflammatory mediators.[8] Being a critical part of the innate immune system, they get activated by stressors or cellular infections. Furthermore, they aid in alleviating the maturation, expression, and release of a wide range of cytokines that are proinflammatory such as pro-IL-18 and pro-IL-1β, which are mainly produced by the cleavage of caspase-1, resulting in a cascade of inflammatory responses.[9,10] Aside from cytokine production, inflammasome activation can also cause pyroptosis, a type of inflammatory death of cells that helps prevent intracellular pathogen proliferation.[11] NLRs, such as galectins, C-type lectins (CTLs), and Toll-like receptors (TLRs), play a crucial role in the innate immune response by detecting pathogenic microbes and other pathogens, forming inflammasomes. Inflammasomes consist of five PRRs, including NLRP4, NLRP3, NLRC1, AIM2, and pyrin. Additionally, NLRP6, NLRP7, NLRP12, and IFI16 from the NLR and PYHIN families can also form inflammasomes. However, the specific composition of these inflammasomes remains unknown[12,13] according to recent data. NLRs possess a tripartite structure, consisting of a central NOD domain flanked by C-terminal leucine-rich repeats (LRRs) and N-terminal domains, either caspase recruitment domains (CARDs) or pyrin domains (PYDs).[9,14] NLRs are classified and named based on their domain structure. They typically contain common domains, including the nucleotide-binding domain, the LRR domain (which aids in ligand binding), and a signaling domain. Notably, all NLRs, except for NLRP10, exhibit these common domains.[15] The signaling region of NLRs facilitates the recruitment of caspase-1, either directly through a CARD domain or indirectly through a PYRIN domain, which can bind to the PYRIN-CARD adaptor ASC.

Among these inflammasomes, the NLRP3 inflammasome has been the subject of much research due to its potential role in various human disorders. The NLRP3 inflammasome's vital role lies in its ability to sense diverse danger signals from infections, the environment, and the host. However, numerous chronic diseases are closely associated with excessive and prolonged NLRP3 inflammasome activation. These encompass autoimmune conditions such as Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and autoinflammatory disorders like Cryopyrin-Associated Periodic Syndromes and Familial Cold Autoinflammatory Syndrome. A range of cardiovascular ailments driven by NLRP3 include gout, atherosclerosis, acute myocardial infarction, silicosis, and non-alcoholic fatty liver disease. Additionally, numerous skin disorders, including acne, atopic dermatitis, and vitiligo, manifest NLRP3-driven mechanisms. The underlying mechanism in these conditions involves upregulated expression

Kanika

Kanika, a third year PhD student in drug delivery, is typically a highly motivated and knowledgeable individual with a strong interest in developing new ways to deliver drugs more effectively to the body. She has gained a deep understanding of the mechanisms of drug delivery and the challenges that come with it. She has been working on various drug delivery nanocarriers that can target the inhibition of various pro-inflammatory markers in mainly two inflammatory disorders – ulcerative colitis and rheumatoid arthritis. She has expertise in the synthesis of various new target specific amphiphiles that can self-assemble and help in the delivery of drugs at site specific locations. She has experience in making various kinds of formulations and their further studies in vitro *and* in vivo*. She is currently working on the synthesis of NLRP3 targeting formulations for therapeutic studies in inflammatory disorders.*

Rehan Khan

Dr Rehan Khan working as a Scientist-D at Institute of Nano Science and Technology (INST), Mohali since 2015. Prior to this, he worked as a post-doctoral fellow at the University of Manitoba, Canada. He obtained his PhD from Hamdard University, New Delhi. The research in his laboratory at INST focuses on the design and development of therapeutic nanomicelles or nano-sized delivery systems for the management of experimental rheumatoid arthritis (RA) and Ulcerative colitis The research also focuses on the development of nanoparticles for the synthetic lethal therapy for colorectal cancer. He is also working on the safety assessment of nanoparticles using rat/mice models. He has published around 90 journal articles and 15 book chapters with a total of 3200 citations, with 34 h-index.

of the NLRP3 gene, amplifying the activity of pro-inflammatory cytokines, thereby triggering inflammation.[16]

The NLRP3 inflammasome exhibits a dichotomous nature, acting as both a friend and a foe in the context of inflammation. The beneficial or pathogenic role of the NLRP3 inflammasome in inflammation remains a subject of debate. Our review disseminates the most recent findings on the nanotechnological approach towards the modulation of NLRP3 inflammasomes. Furthermore, it also includes an inflammatory cascade that affects the activation and assembly processes of NLRP3 signalling. By consolidating current knowledge, our review enhances the understanding of the intricate role of nanotechnological interventions in precisely modulating the NLRP3 inflammasome across diverse inflammatory contexts. This review will benefit researchers using nanocarriers as a therapeutic approach to target inflammasomes and treat inflammatory-based diseases.

2. NLRP3 inflammasome

2.1 Biological characteristics of the NLRP3 inflammasome

As discussed above there are many types of inflammasomes, but among them, the one that is the most characterized is the NLRP3 inflammasome, which aids in strategically targeting the inflammatory disease. The NLRP3 inflammasome mainly consists of a three-component protein assembly that includes procaspase-1, adaptor protein apoptosis-associated speck-like protein (ASC), and lastly, NLRP3 protein.[17–19] The pyrin domain-containing protein 3 (NLRP3) of the NLR family is the receptor that helps in recognizing the pattern that is activated by numerous stimuli, including lipopolysaccharide (LPS) and ATP-rich, crystalline, high fat, and high sugar meals.[20,21] The NACHT domain and LRRs have a relationship under normal conditions, which prevents the formation of inflammasomes by inhibiting the interaction between the ASC and NLRP3 protein.[22] The structure of the NLRP3 protein is modified in response to PAMPs, DAMPs, and other exogenous invaders or environmental stress to enhance the interaction between PYDs in the ASC and NLRP3 protein. After the interaction of the NLRP3 protein with ASC, procaspase-1, another NLRP3 inflammasome component, binds to ASC through CARD that is part of procaspase-1 binding to the homologous area of ASC forming the NLRP3 inflammasome. The development of the protein complex causes the self-cleavage of procaspase-1, resulting in the active tetramer named caspase-1 p10/p20, which leads to the maturation of cytokines like IL-18 and IL-1β that are found to be pro-inflammatory in nature by converting their pro-forms into active forms, persuading inflammatory and immune responses.[23–26]

2.2 Signalling mechanism of the NLRP3 inflammasome

Despite mounting evidence of the NLRP3 inflammasome's critical involvement in the innate immune system, the methods by which NLRP3 reacts to numerous stimuli and events at both cellular and molecular levels to cause the NLRP3 inflammasome to assemble remain a mystery. The canonical and non-canonical inflammasome pathways are briefly outlined in order to explain how the activation of NLRP3 inflammasomes takes place.[27]

2.2.1 Canonical pathway. Rather than attaching directly, NLRP3 reacts to stimuli-induced cellular processes through the serine/threonine-protein kinase NEK7. The creation of a conventional NLRP3 inflammasome has been described using a two-signal paradigm. In this concept, microbial components or endogenous cytokines stimulate the NLRP3 inflammasome, which is triggered by ATP as a second signal.[28,29]

(A) Priming step. Various priming stimuli activate the transcription factor NF-κB, which gives the initial signal for inflammasome activation, causing macrophages to upsurge NLRP3 and pro-IL-1β production. The existence of priming stimuli, on the other hand, is insufficient to activate the inflammasome. Although upregulating NLRP3 may increase inflammatory responses, current research has shown that the priming phase promotes NLRP3 inflammasome activation at the transcriptional level but is not required for activation of other inflammasomes.[30,31]

(B) Secondary step. Following the priming process, NLRP3 may be triggered by a diversity of chemicals and organisms, including bacteria. Due to differences in their structure and biology, NLRP3 cannot directly interact with these agonists. As a result, current research assumes that the NLRP3 inflammasome is activated by shared signaling events generated by NLRP3 agonists at the molecular and cellular levels, such as ROS generation, ionic flux, and lysosomal damage.[32]

(C) Ion flux. Ion mobilization in multiple intracellular signaling pathways has long been thought to occur when NLRP3 activators are stimulated. Even before inflammasomes were found, there was a strong link between IL-1β maturation and potassium (K^+) efflux.[27,33] Despite the difficulty in identifying the channel, the fluxion of K^+ across the plasma membrane is widely accepted as a common cause of the activation of the inflammasome. Furthermore, excessive levels of extracellular K^+ can prevent activation.[34] Moreover, the inflow of Na^+ and Ca^{2+},[35] as well as the outflow of Cl^-, is thought to be an upstream event in the activation of the NLRP3 inflammasome. They also take part in a number of signaling pathways that are implicated in inflammasome activation. Ion channels are future aims for anti-inflammatory treatment, despite the fact that the specific mechanism by which numerous ions coordinate in inflammasome activation is yet unknown.

(D) ROS production. Membrane damage, hypoxia, and other stressful situations have all been linked to the formation of reactive oxygen species (ROS), which has been considered another standard signal of NLRP3 inflammasome activation. Inflammatory disorders are related to disrupted mitochondrial ROS (mtROS) formation. The mitochondrial respiratory chain is inhibited, which in turn inhibits autophagy that causes the formation of ROS, which can activate the NLRP3 inflammasome. The fact that NLRP3 and ASC are both found in the mitochondria backs up this claim.[36]

(E) Lysosomal damage. Lysosomal damage, which is induced by the absorption of particles that are both endogenous and exogenous such as alum, calcium crystals,[37] silica, and cholesterol crystals,[38] is another primary source of inflammasome activation. After the particulate matter is endocytosed and lysosomal contents are spilled into the cytosol, lysosome disruption occurs as a crucial step in the secondary phase of NLRP3 inflammasome activation. Hornung[39] showed this inflammatory process by stating that phagocytosis induced by crystal and lysosomal instability might stimulate the NLRP3 inflammasome.

2.2.2 Non-canonical pathway. The finding of caspase-11-dependent pyroptosis and activation of non-canonical inflammasomes in murine macrophages led to the development of the non-canonical pathway.[40] Furthermore, most of the bacteria that are Gram-negative in nature, including *Citrobacter rodentium* and *E. coli*, may activate this pathway. Caspase-4 and caspase-5 are caspase-11's human equivalents.[25] It is worth noting that caspase-11/-5/-4 activation is independent of a PRR-mediated inflammasome.[41] In Gram-negative bacteria, LPS may enter the cytosol either by outer membrane vesicle-mediated entry or through the process of endocytosis.[42] By promoting caspase-11 transcription, these events operate as a priming signal for the activation of this particular inflammasome pathway. If the gut's unique physiological milieu, particularly intestinal oxidant–antioxidant homeostasis, is disrupted, the NLRP3 inflammasome may become overactive. These disturbances may eventually lead to the onset of inflammatory bowel disease (IBD).[43] Fig. 1 illustrates both the canonical and non-canonical NLRP3 signaling pathways, encompassing the role of the innate immune system in initiating the canonical pathway through primary and secondary steps.

3. Interplay between the NLRP3 inflammasome and factors affecting inflammation

Inflammasome components combine and oligomerize in response to infection and/or damage, causing procaspase-1 to auto-cleave into its active form. Proinflammatory cytokines are transformed into mature forms by activated caspase-1, which subsequently contribute to the inflammatory response.[44] The sensor PRRs recognize the danger or stressor, which triggers the activation of NLRP3. PPRs may detect PAMPs such as bacterial secretion systems and parts of microbial cell walls and microbial nucleic acids.[45,46] Furthermore, uric acid crystals and ATP that come under the category of DAMPs aid in triggering the PPRs. Being the two-stage process of its activation, the first step is the detection and production stage, which starts with TLRs recognizing DAMPs and PAMPs. TLRs identify numerous stress stimuli and trigger NF-κB signaling, which leads to increased creation of precursor proteins such as pro-IL-18, NLRP3 protein, and pro-IL-1β.[47] The assembly and effector stage, which commences with the assembly of the NLRP3 inflammasome, is the second step. The mature complex is formed by procaspase-1, NLRP3 protein, and ASC, which changes the immature versions of IL-1β and IL-18 into their mature forms. The ensuing inflammatory response is mediated by IL-18 and IL-1β.[48] Furthermore, other danger signals, including mitochondrial dysfunction (MtD). Nitric oxide (NO), calcium, and ROS can activate the NLRP3 inflammasome. ROS are produced in the cell by two sources: cytosolic ROS and mitochondria-derived ROS (mtROS). Following the identification of PAMPs from microorganisms or DAMPs, mtROS can operate as a second messenger to activate inflammasomes.[49] The appropriate functionality of mitochondria is also required for the stimulation of the NLRP3 inflammasome. MtD can be influenced by a series of causes, including NO and Ca2+, which can trigger the NLRP3 inflammasome by releasing oxidized mitochondrial DNA (mtDNA) following TLR engagement.[50] Several studies evaluated the different signals or stimuli that have been activating the NLRP3 inflammasomes. The NLRP3 inflammasome is involved in the development of atherosclerosis by driving the production of IL-1β. Through the NLRP3 inflammasome, hydroxyapatite crystals can activate IL-1β and increase its production in osteoarthritis, triggering inflammation and joint disorders. The NLRP3 inflammasome and ROS signaling may be activated by pulmonary macrophages which become active when endocytosis of silica and asbestos takes place and further cause silicosis and asbestosis.[51] The specific signaling mechanism behind the cross-talk between ROS in NLRP3 remains unknown; rather, it has been recognized extensively. Furthermore, we explore the rapidly expanding cross-talks between the inflammasome and various factors that affect inflammation. Fig. 2 provides a comprehensive overview of NLRP3's involvement in inflammation, highlighting how the assembly of NLRP3 adapts in response to infections, giving rise to diverse PAMPs, DAMPs, and other activating factors.

4. Cross-talk between the NLRP3 inflammasome, caspase-8 and caspase-11

Current research has revealed that caspase 8 plays a crucial role in the activation of inflammasomes, cell death, and production of IL-1β in response to a variety of ligands. Another research showed that inhibiting caspase-8 decreased NLRP3 and AIM2-induced caspase-1 activation, indicating that caspase-8 plays a role in inflammasome activation.[52] In response to AIM2 and NLRP3, recruitment of caspase-8 through ASC causes its activation, which leads to apoptosis. Although pyroptosis is found to be a process of rapid cell death, this work indicated that cells missing caspase-1 suffer apoptosis that will be *via* caspase-8 with slower kinetics.[53]Despite the fact that caspase-8 is a recognized predictor of cell survival or death *via* apoptosis, recent investigations have assigned it a critical role in inflammasome acti-

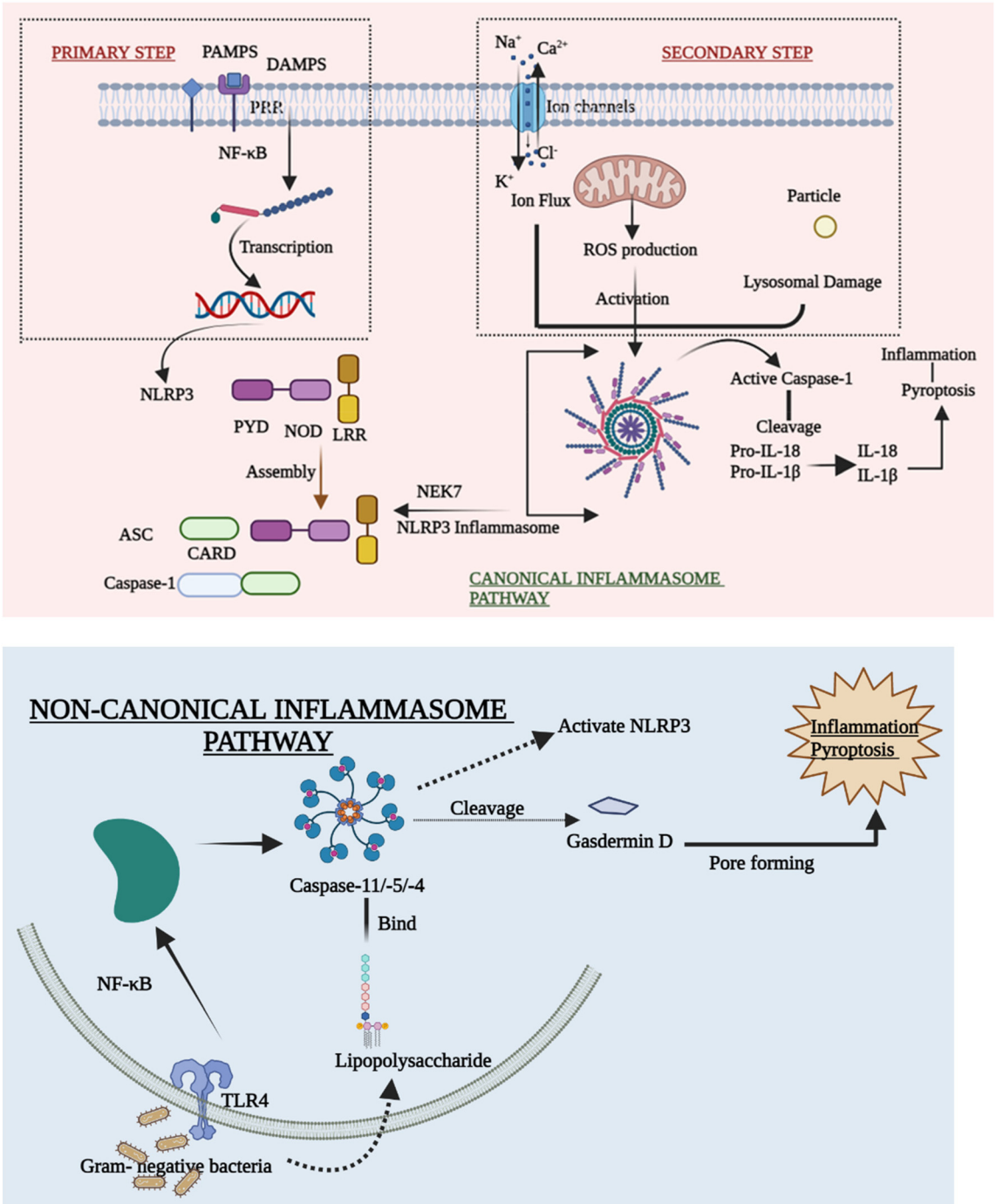

Fig. 1 A priming signal, denoted as Signal 1 or "S1", is essential to initiate classical NLRP3 inflammasome activation and induce NLRP3 gene expression. This initial activation often involves Toll-like receptors (TLRs), engaging NF-κB signaling. Pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) provide an activating stimulus, referred to as Signal 2 or "S2". NLRP3 recognizes these cellular perturbations, initiating the assembly of the NLRP3 inflammasome. This assembly process involves NEK7 kinases, ASC adaptor, and caspase-1 enzyme. Subsequently, this culminates in gasdermin cleavage, liberating proinflammatory cytokines IL-1β and IL-18. In the context of Gram-negative bacteria, the non-canonical NLRP3 inflammasome can be triggered. Recognition of Gram-negative bacteria's lipopolysaccharide (LPS) by Toll-like receptor 4 (TLR4) *via* TRIF adaptor induces type I interferon (IFN) production. Additionally, LPS activates caspase 11, leading to gasdermin D cleavage and consequent cellular swelling, or proptosis. Abbreviations: TLR-4 – toll-like receptors; NF-κB – nuclear transcription factor kappa B; NLRP3- NOD-, LRR- and pyrin domain-containing 3; PYD – pyrin domain; LRR – leucine-rich repeats; PAMPS – pathogen-associated molecular patterns; DAMPs – danger-associated molecular patterns; PRR – pattern recognition receptors; and NEK7 – serine/threonine-protein kinase.

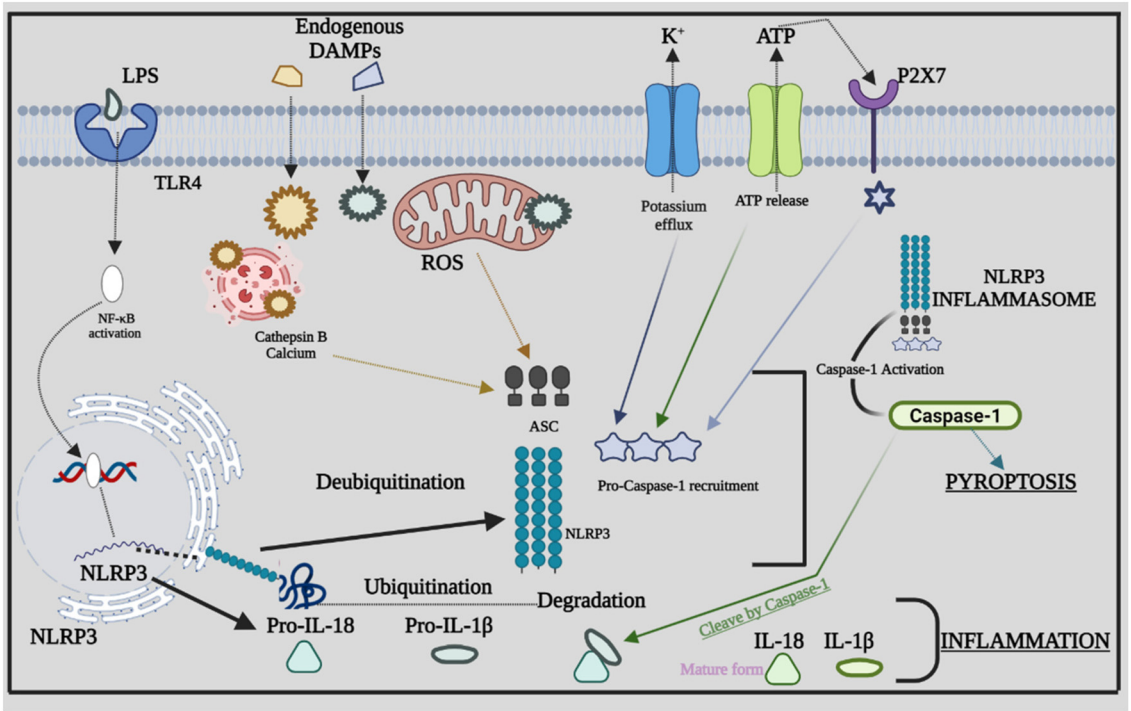

Fig. 2 Relationship between activation of NLRP3 and inflammation. It is activated by various endogenous DAMPs that include cholesterol crystals, uric acid crystals, free fatty acids, *etc.* Various events that get activated after recognition of DAMPs are ROS generation, intracellular ATP release, deubiquitination of NLRP3, lysosomal rupture and release of cathepsin calcium that leads to the formation and activation of the NLRP3 complex. Therefore, activated caspase-1 induces pyroptosis, cleaves the precursor of pro-inflammatory cytokines and generates active cytokines IL-18 and IL-1β. Abbreviations: ROS – reactive oxygen species; LPS – lipopolysaccharide; ATP – adenosine triphosphate; and P2X7-receptor-mediated efflux of potassium.

vation. Talking next about caspase 11, it was later discovered to be an independent inducer of pyroptosis, without the need for caspase 1 as well as the need for activation of NLRP3 through the CARD domain of Gram-negative bacteria.[54] Caspase-11 was found to be serving as a sensor and a persuader of LPS-induced pyroptotic reactions, as well as aids in triggering the NLRP3 inflammasome's assembly. This differentiates between the bifunctional roles of activation of inflammasome pyroptosis that is triggered by caspase-11 activation, and on the other hand, processing of the cytokine that is triggered by NLRP3-mediated caspase-1 activation.[55] Fig. 3 elucidates the pivotal role of caspases in inflammation, illustrating their impact through the NLRP3 signaling pathway, ultimately culminating in the production of IL-1β, a potent proinflammatory cytokine, thus driving the inflammatory response.

5. Cross-talk between the NLRP3 inflammasome and autophagy

To restrict the infection and improve pathogen clearance, cells initiate autophagy in response to a pathogen. The relationship between autophagy, inflammasome activation, and cytokine processing was initially demonstrated by Saitoh *et al.*[56] Autophagy also removes damaged organelles that are produced as a result of homeostatic circumstances, reducing the inflammasome response.[57,58] Blocking autophagy enhances inflammasome activation by accumulating ROS-producing mitochondria. On the other hand, autophagy malfunction can result in disorders characterized by hyper inflammation and excessive activation of the NLRP3 inflammasome, making it a key regulator of inflammasomes. Enhanced ROS generation in mitochondria caused *via* suppression of complex I and III of mitochondria results in boosted activation of caspase 1 that is NLRP3-dependent and release of IL-1β in both macrophages and monocytes, according to Zhou *et al.*[59] inflammasome activation is also elevated in cells that have missing components of autophagosome formation, such as beclin-1, ATG16L, and LC3B. Furthermore, IL-1β stimulates autophagy, implying a negative feedback loop for inflammasome activation.[57,59,60] The NLRP3 inflammasome has been found to interrelate with the machinery of autophagy so that co-localization with autophagosomes takes place. This further leads to an increase in NLRP3 inflammasome activation when the autophagic route is inhibited. This shows that post-translational changes of NLRP3 (such as phosphorylation and ubiquitination) and subsequent autophagic clearance of inflammasome components after activation function as a negative-feedback loop to prevent an over-inflammatory response. Ubiquitination and phosphorylation changes of NLRP3 and clearance of autophagic

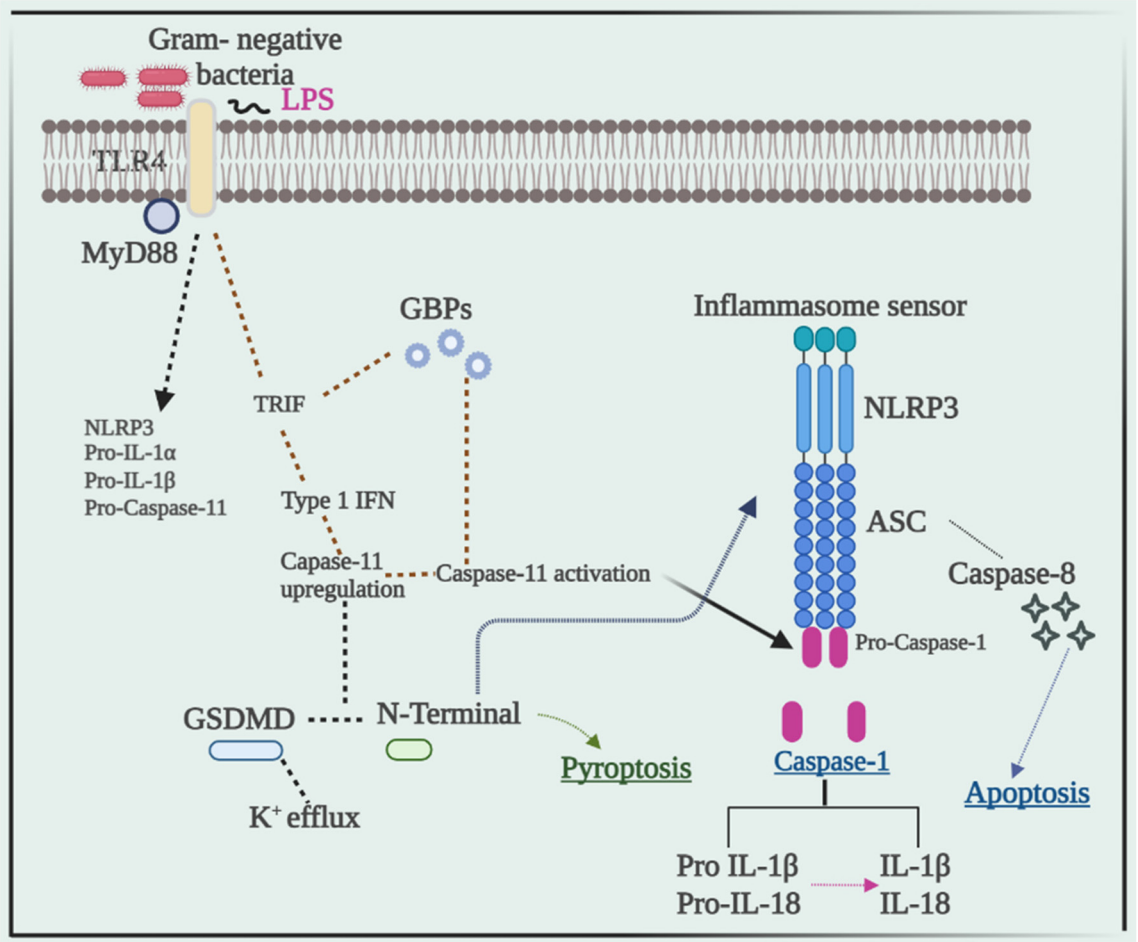

Fig. 3 Crosstalk between activation of NLRP3 and different caspases. The interplay between NLRP3 activation and various caspases involving distinctive mechanisms. Upon sensing the cytosolic lipopolysaccharide (LPS), caspase-11 becomes engaged, resulting in NLRP3 inflammasome assembly. A TLR4-TRIF-type I interferon (IFN) signaling pathway orchestrates the upregulation of caspase-11 and activation of guanylate binding proteins (GBPs), pivotal for vacuolar lysis, thereby liberating LPS. Caspase-11, operating through a yet-to-be-elucidated mechanism, directly cleaves gasdermin D, prompting pyroptosis and triggering NLRP3 activation. In parallel, the activation of caspase-1 precipitates the maturation of pro-IL-1β and pro-IL-18, culminating in pro-inflammatory cytokine release. Abbreviations: TRIF – TIR domain-containing adaptor protein; GSDMD – gasdermin D; and GBPs – guanylate binding proteins.

components after it gets activated act as the negative-signal loop to avoid any response that would be over-inflammatory.[61–64] Fig. 4 briefly outlines the interplay between cellular autophagy initiation inhibition and the activation of NLRP3. This reciprocal relationship demonstrates the dual and contentious nature of the process.

6. Cross-talk between NLRP3 inflammasomes and the gut microbiota

The ecology of the gut microbiota, which impacts the activation state of inflammasomes, may be affected by diet and aseptic procedures utilized by various facilities. Endogenous danger signals such as dietary cholesterol and deoxycholic acid activate the NLRP3 inflammasome, contributing to colorectal cancer (CRC) and high fat diet (HFD-related colonic inflammation. Inflammation is reduced when NLRP3 is activated by short-chain fatty acids or inhibited by omega-3 fatty acids.[65–68] The NLRP3 inflammasome affects the gut microbiota, according to several studies. Animal models have been used to investigate the function of commensal microorganisms in NLRP3 activation in the etiology of inflammatory disorders. Skin commensal microorganisms activate the NLRP3 inflammasome in the CAPS mouse model Nlrp3R258W, which promotes cutaneous inflammation. Certain commensal pathobionts in the gut have been shown to be capable of activating the NLRP3 inflammasome in intestinal mononuclear phagocytes.[69] The activation of NLRP3 by *P. mirabilis* is essential for the worsening of colitis produced by this bacterium's colonization. Kitamoto and his group found that ingested *K. aerogenes* enters the gastrointestinal system, and its ectopic gut coloniza-

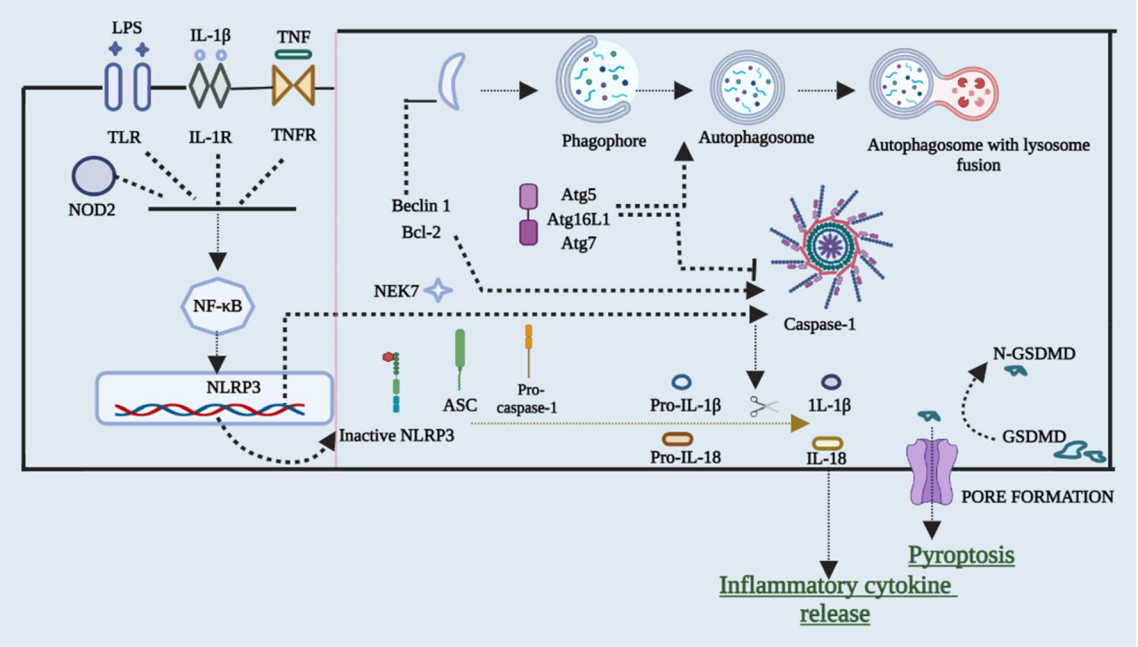

Fig. 4 Cross-talk between autophagy and NLRP3 inflammasome activation. Its role always remains controversial. Inhibition of autophagy related genes namely Atg7 and Atg16L1 suppresses the activation of NLRP3 and hence suppresses inflammation. On the other hand, suppressing the gene Beclin 1 is vital for the activation of the NLRP3 inflammasome and hence the recruitment of caspase-1 will take place and cause the release of a proinflammatory cytokine that leads to inflammation. Abbreviations: BCL 2 – B-cell lymphoma 2; ATG – autophagy related protein.

tion exacerbates intestinal inflammation in DSS-induced colitis and Il-10-deficient animals.[70] As a result, growing evidence suggests that the NLRP3 inflammasome and downstream mediators like IL-18 and IL-1β play a vital role in the initiation and development of intestinal inflammation. Furthermore, pathobiont-refereed stimulation of the NLRP3 inflammasome may play a critical role in the onset or worsening of intestinal inflammation. These conclusions point to a dynamic and growing link between the daily routine diet, microbiota, and inflammasome activation, implying that dysbiosis affected by inflammasomes should be examined and interpreted with caution.[71,72] Conclusively, Fig. 5 elucidates the intricate interplay between intestinal inflammation and NLRP3 signaling. It highlights the significant involvement of the gut microbiota in triggering inflammasome assembly, underscoring their role in this context.

7. Cross-talk between NLRP3 inflammasome activation and bacterial infection

Gram-positive *Listeria monocytogenes* and *Staphylococcus aureus*, Gram-negative *Shigella flexneri and Shigella sonnei*, but not Gram-negative *Francisella tularensis* and *Salmonella typhimurium*, all stimulate NLRP3-dependent IL-1β production, according to previous research that was demonstrated to activate the inflammasome named NLRP3.[73] The primary murine macrophages that have been LPS primed depict that *S. sonnei* promoted the production of IL-1β *via* P2X7 receptor-mediated efflux of potassium, ROS formation, acidification of lysosomes, and mitochondrial damage.[74] In human monocytes and macrophages, live intracellular *Mycobacterium tuberculosis* infection resulted in NLRP3-dependent IL-1β production and pyroptosis.[75,76] Infection of human macrophages with *Salmonella typhimurium* triggered the NLRP3 inflammasome in an indirect manner. *Salmonella* sequestration within the vesicles that contain *Salmonella* is caused by *S. typhimurium* infection, which finally gets burst by releasing its pathogens into the cytosol. In addition, the NLRP3 inhibitor only decreased the release of cytokine IL-1β and pyroptosis in macrophages when NLRC4 activity was inhibited simultaneously.[77]

8. NLRP3 inhibitors: promising therapeutic candidates

The oligomerization of NLRP3 and subsequent ASC alignment onto NLRP3 oligomers are essential steps in the formation of the NLRP3 inflammasome complex. Through the recruitment and oligomerization of ASC, the ATPase activity of NLRP3's NACHT domain drives the oligomerization of NLRP3, culminating in caspase 1 activation. In light of this, inhibitors specifically targeting NLRP3 within the inflammasome hold substantial promise as therapeutic targets.[78]

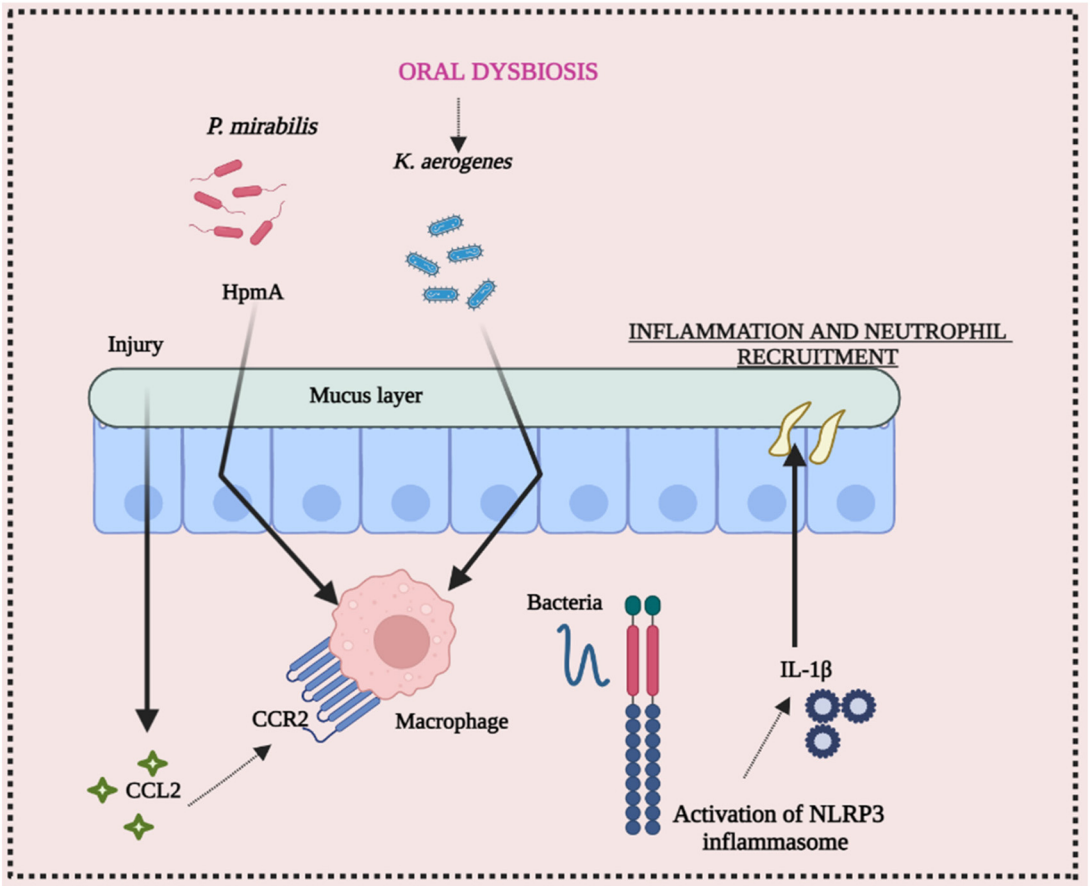

Fig. 5 Cross-talk between activation of the NLRP3 inflammasome and intestinal microbiota. Production of the pro-inflammatory cytokine IL-1β and activation of the NLRP3 inflammasome resulting in the aggravation of inflammation of the intestine. Commensal bacteria *Proteus mirabilis* produced hemolysin that helps in the activation of the NLRP3 inflammasome in newly recruited monocytes CCR2 + Ly6C^{high} *via* hemolysin A. Hence, it depicts the role of the gut microbiota in the activation of NLRP3 and therefore causes inflammation. On the other side *Klebsiella aerogenes,* the oral pathobionts that are ectopically colonized were found to activate the NLRP3 pathway in intestinal macrophages. Abbreviations: *K. aerogenes* – *Klebsiella aerogenes*; Hpma – hemolysin A; and *P. mirabilis* – *Proteus mirabilis*.

(A) MCC950: MCC950, a potent compound, exhibits direct interaction with the Walker B motif within the NLRP3 NACHT domain. This interaction leads to the inhibition of NLRP3 inflammasome activation, concurrently impeding ATP hydrolysis, ASC oligomerization, and chloride ion export.[79] The remarkable *in vivo* efficacy of MCC950 has been substantiated across diverse disease models. Notably, MCC950's inhibitory impact remains unaffected by NLRP3 inflammasome activation, NLRP3–NLRP3 interactions, calcium signaling, mitochondrial respiration, ROS generation, potassium efflux, or NEK7–NLRP3 interactions. The therapeutic utility of MCC950 in addressing inflammatory disorders and related complications has been firmly established.[80]

(B) OLT1177: OLT1177, an oral sulfonyl cyanide compound, exerts inhibitory effects on ASC oligomerization and reduces ATPase activity by directly binding to NLRP3. Moreover, OLT1177 disrupts the interaction between NLRP3 and ASC, effectively impeding the assembly of the NLRP3 inflammasome. Consequently, OLT1177 emerges as an orally administrable therapeutic agent, boasting notable benefits for inflammatory disorders attributed to its minimal toxicity and limited adverse effects.[81,82]

(C) INF39: INF39 stands out as a non-toxic, enduring, and selective inhibitor of the NLRP3 inflammasome, effectively impeding NLRP3 activation. INF39's anti-inflammatory effects predominantly stem from its capacity to hinder the NEK7–NLRP3 interaction. This initial inhibition subsequently halts the oligomerization process of NLRP3, further extending to the oligomerization of ASC, culminating in the prevention of speckle formation.[83]

(D) Tranilast: Tryptophan metabolite, tranilast, effectively hampers NLRP3 inflammasome activation. Notably, this inhibition occurs without compromising K+ efflux, ATPase role, or mitochondrial integrity. Tranilast's mechanism involves binding to the NACHT domain, consequently obstructing NLRP3 oligomerization and the ensuing assembly of the NLRP3 inflammasome. This interruption curbs caspase-1 activation and subsequent IL-1β synthesis.[84]

(E) CY-09: An alternate NLRP3 inhibitor engages in direct binding with the ATP binding motif within the NACHT

domain of the NLRP3 assembly. Unlike its impact on the mitochondrial integrity, potassium efflux, or chloride ion efflux during NLRP3 activation, this inhibitor distinctly targets and suppresses NLRP3 ATPase activity.[85]

(F) JC124: JC124, a selective NLRP3 inflammasome inhibitor, centers its attention on ASC oligomerization within macrophages. This compound demonstrates not only activity but also constitutive expression of the active NLRP3 inflammasome. Across multiple investigations, JC124 exhibited its inhibitory prowess by strategically targeting oligomerization, thereby effectively combating inflammation.[86]

(G) 3,4-Methylenedioxy-β-nitrostyrene (MNS): MNS decreases the NLRP3 ATPase activity, resulting in the inhibition of NLRP3 inflammasome activation. Importantly, MNS achieves this inhibition without disrupting K+ efflux or impeding the activation of NLRC4 or AIM2 inflammasomes.[87]

Consequently, these inhibitors have been comprehensively documented for their direct interference with NLRP3 assembly, paving the way for the formulation of inflammation-targeted strategies utilizing them as potential anti-inflammatory drugs.

9. Nanotechnological approach towards the butterfly nature of the NLRP3 inflammasome

The NLRP3 inflammasome can impact various inflammatory disease pathogenesis and control the production of proinflammatory cytokines, including IL-1β and IL-18. Whether the NLRP3 inflammasome is beneficial or harmful to diseased patients remains a point of contention. Recently the growing body of studies examined the pathogenic and preventive functions of the NLRP3 inflammasome and the underlying mechanism of their regulation by different nanocarriers.

9.1 Drug delivery nanocarriers targeting the upregulation of the signalling cascade of the NLRP3 inflammasome : pathogenic role

Nanoparticle-associated molecular patterns, mediated by synthetic materials like nanoparticles and nanomaterials, have lately been postulated as NLRP3 inflammasome danger signals. These nanoparticles are absorbed into immune cells, which activates them by causing tissue damage. In skin keratinocytes, monocytes, and hepatoma cells, many metal oxide, and metal-based nanoparticles have been shown to initiate the NLRP3 inflammasome. Particulate stimulants activate the NLRP3 inflammasome, which has been linked to the pathophysiology of a diversity of inflammatory disorders.

9.1.1 Metal nanoparticles targeting the inflammatory cascade

(A) Palladium and silver nanoparticles. Metal nanoparticles are frequently exposed to oral epithelial keratinocytes. In addition, Eri *et al.* discovered that palladium and silver nanoparticles diminish the number of acidic organelles and cathepsin B expression in oral keratinocytes, indicating that NLRP3 inflammasome stimulation by metal-based nanoparticles is linked to lysosomal injury.[88] In summary, ingestion of metal-based nanoparticles into human oral keratinocytes caused autophagic-lysosomal related dysfunctions and activated the specific inflammasome that is NLRP3. Metal nanoparticles might be integrated into oral keratinocytes and trigger the NLRP3 inflammasome, as well as immune cells, according to Eri's findings.

According to recent research, depending on the nanoparticle surface charge and size, modification of surface-produced nanoparticles activated the NLRP3 inflammasome and boosted the production of antibodies. Improved uptake of inflammasome activators, more ROS production, repressed degradation of inflammasomes due to the cooperative activity of lysosomes, and other dangerous signal releases that are presently anticipated mechanisms of nanoparticle-induced activation of NLRP3.[89–92]

Another relevant study on silver nanoparticles elucidated that AgNPs are thought to cause cytotoxicity by triggering apoptosis and non-apoptotic cell death, according to growing research.[93] They discovered that particle sizes that include 10, 50, and 100 nm of AgNPs cause cytotoxicity in liver cells, which is facilitated *via* AgNP-induced lysosomal membrane permeabilization and inflammasome-dependent stimulation of caspase-1.[94] This proinflammatory protease governs cell death. AgNPs activated caspase-1 in HepG2 cells, and inhibiting the autophagy-lysosomal pathway exacerbates NLRP3 inflammasome-dependent caspase-1 activation, according to their findings. AgNPs can promote autophagy and caspase-1 activation even at low, non-cytotoxic concentrations, according to their conclusions.[95] The findings of Mishra and his group have shown that limiting lysosomal acidification or inhibiting siRNA-mediated autophagosome formation exacerbates activation of AgNP-induced caspase-1 and the death of the cell. The results show that autophagy may have a protective function in AgNP-induced activation of inflammasomes at subcytotoxic concentrations. Caspase-1 activation and cell death are exacerbated when AgNP-induced autophagy is blocked. AgNPs cause autophagy and permeabilization of the lysosomal membrane, resulting in caspase-1 activation *via* the NLRP3 inflammasome.[96]

(B) Gold nanoparticles. Gold (Au) nanoparticles activate innate immune signaling pathways in a size-dependent manner, according to this study. The NLRP3 inflammasome is preferentially activated by ultrasmall Au nanoparticles (10 nm) for maturation of caspase-1 and interleukin-1 generation, whereas the NF-κB signaling pathway is activated by more significant Au nanoparticles (>10 nm). Au nanoparticles (Au 4.5) that are ultrasmall (4.5 nm) trigger the NLRP3 inflammasome by directly penetrating into the cytoplasm of the cell, promoting strong ROS production and targeting protein-LC3 (microtubule-associated protein 1-light chain 3) in an endocytic independent manner for proteasomal degradation. Autophagy relies on LC3, which is needed for limiting the activation of NLRP3 and plays an important role in inflammasome negative regulation.[97]

(C) Silica dioxide and titanium dioxide nanoparticles. Previously reported literature showed that both in *in vitro* and *in vivo* cases, titanium dioxide (TiO_2) nanoparticles cause the development of ROS along with inflammation. In the presence of titanium dioxide, the pyrin domain of the NLRP3 inflammasome, a nucleotide receptor, is activated, which was already known.[92,98] Ruiz and his group revealed that the NLRP3 inflammasome was implicated in the worsening of acute colitis when TiO_2 nanoparticles were given orally. Crystals were found to be accumulated in the spleens of mice that had been administered with TiO_2 nanoparticles. TiO_2 particles were taken up by macrophages and human intestinal epithelial cells (IECs) *in vitro*, resulting in the assembly of NLRP3-ASC-caspase-1, then the cleavage of caspase-1, and finally the release of proinflammatory interleukins 18 and 1β.[99]

Another group, Baron's, recently showed that nanoparticles of SiO_2 (nano-SiO_2 and TiO_2 (nano-TiO_2) were detected by NLRP3 and caused the secretion of mature IL-1β, similar to asbestos or silica in the environment. However, its mechanism of activation of inflammasome is still unclear. Furthermore, they found that inflammasome activation requires the active release of ATP, ADP, and adenosine receptor signaling. P2Y1, P2Y2, A2A, and A2B receptor expression in NLRP3 was significantly increased by nano-SiO_2 or nano-TiO_2. However, P2X7 receptor expression was significantly decreased.[100,101] Surprisingly, increased ATP and ADP hydrolysis boost IL-1β production in response to nanoparticles, whereas adenosine degradation or specific A2A or A2B receptor blockade suppresses it. Nanoparticles stimulate the NLRP3 inflammasome *via* activating PLC-InsP3 and/or inhibiting adenylate cyclase (ADCY)-cAMP pathways downstream of these receptors, according to their findings.[102] By blocking adenosine kinase activity, nucleotide receptors, and nucleoside transporters, their results may lead to novel therapeutic methods for controlling chronic inflammation. These findings offer fresh insights into the processes of NLRP3 inflammasome activation as well as novel anti-inflammatory treatment methods.[103]

Kim and his group reported another relevant study on the same metal nanoparticle named TiO_2 NPs that have been demonstrated to cause oxidative stress and inflammation in HepG2 and Caco-2 cells in previous research. In addition to in the respiratory system, TiO_2 NPs have also been demonstrated to induce ROS, apoptosis, and inflammation.[104] Kim *et al.* stated that TiO_2 NPs had been shown to trigger the inflammasome pathway, causing lung tissue injury. This pathway's activation damages tissue and leads to the development of liver and intestinal disorders. The primary component of this route is the NLR family pyrin domain containing 3 (NLRP3), which triggers caspase-1. When this caspase is activated, pro-IL-1β is activated, resulting in tissue damage and inflammation, and it also becomes a part of the pathogenesis of various disorders like chronic liver disease. The findings of this investigation revealed that the administration of TiO_2 NPs causes inflammation, oxidative stress, and apoptosis in the liver and intestine in a dose-dependent way, which was substantially accompanied by histological alterations in the liver and intestine.[105]

(D) Silica nanoparticles. Some metal nanoparticles are found to be crucial for human applications. Silica nanoparticles (SiNPs) have various human applications as they can induce multiple immune responses.[106]The findings of Gomez *et al.* showed that both 200 nm and 12 nm SiNPs cause PBMCs to produce IL-1β and IL-6, consistent with earlier research. The main results show that SiNPs cause inflammasome components (NLRP3, ASC, Casp-1), as well as IL-1b, IL-6, and IL-18, to be expressed in PBMCs and neutrophils in a dose-dependent way.

In summary, the findings of Gomez and the group showed that SiNPs stimulate the creation of proinflammatory cytokines in a dose-dependent manner and that this stimulation occurs regardless of the NP size. Although results imply that the NLRP3 inflammasome is involved in the generation and release of IL-1β, both 200 nm and 12 nm silica nanoparticles are used at low doses and show mild inflammation action; hence, this might be highly valuable for biological applications.[107]

In addition to this study, in the year 2021, Yang Song and his group revealed that silica nanoparticles (SiO_2 NPs) have been reported to enter the bloodstream *via* inhalation and cause inflammation of vascular endothelial cells. They discovered that amorphous SiO_2 NPs cause signal axis modulation in human umbilical vein endothelial cells (HUVECs), which leads to proinflammatory responses. HUVECs exposed to SiO_2 NPs produce increased expression of inflammatory cell factors.[108]

Furthermore, recently they found that amorphous SiO_2 NPs produce excessive ROS that activates the NLRP3 inflammasome, speeds up the lysine acetylation of HMGB1, enhances its translocation, and release from the nucleus to the cytoplasm, and ultimately causes inflammatory injury in HUVECs *via* TLR4/MyD88/NF-κB signaling pathways.[108]

Later, increased medicinal uses of mesoporous silica nanoparticles (MSNs) have sparked interest in their toxicological consequences; nonetheless, MSN toxicity is still unclear, as are the underlying processes.[109] MSNs exhibited dose- and time-dependent cytotoxicity in hepatic L02 cells. NLRP3 inflammasomes in hepatocytes were then activated by MSNs, causing caspase-1-dependent pyroptosis, a new model of cell death.[110,111] Furthermore, tests revealed that MSNs increased the production of ROS in mitochondria and that a ROS scavenger may reduce MSN-induced NLRP3 inflammasomes and pyroptosis in the liver. The findings of Zhang and his group revealed that MSNs generated hepatocyte pyroptosis and inflammation of the liver by activating NLRP3 inflammasomes, which was driven by MSN-induced ROS production. Their group research also revealed new information on MSN hepatotoxicity and the processes that underpin it, as well as a viable strategy for improving MSN biosafety.[112]

Something had to be done to lower the toxicity of metal nanoparticles. Another group thought of surface modification of nanoparticles that became an emerging method for "masking" the harmful effects of nanoparticles, and it has been found to minimize non-specifically that further reducing its aggregation.[113] Surface modified silica nanoparticle (SiO_2

NPs) lowers their possibility for activation of inflammasome and its cytotoxicity, according to *in vitro* investigation.[114,115]

Furthermore, the previous group elucidated that surface-modified SiO_2 NPs reduce the immunomodulatory and proinflammatory effects in the murine ovalbumin (OVA)-induced allergic airway inflammation model.[116] Viviana *et al.* studies proved various studies regarding the impact of surface-modified Si nanoparticles, both *in vitro* and *in vivo* based studies. It has been found that surface-modified SiO_2 NPs with the combination of both amino ($-NH_2$) group and phosphonate (–P) significantly lessen the activation of inflammasome in murine bone marrow-derived dendritic cells (BMDCs), according to their findings rather than plain SiO_2 NPs. Plain SiO_2 NPs were not found to activate the inflammasome in non-sensitized mice (NS) but in sensitized (S) animals; when administered with PEGylated (-PEG), SiO_2-NPs showed higher IL-1β and caspase-1 mRNA expression. Furthermore, phosphonate and amino modification, but not PEGylation, significantly lessen the expression of genes that are inflammatory in nature in the lungs of both S and NS mice when given SiO_2 plain NPs intratracheally.[117] The majority of the investigations have concentrated on discovering and reporting inflammasome-activating nanoparticles such as silver, SiO_2, mesoporous silica, DOTAP, iron oxide, carbon black, and TiO_2 particles.[103,118–120]

(E) Zinc oxide nanoparticles. Several *in vitro* and *in vivo* investigations have found that zinc-oxide nanoparticle (ZnO-NPs) exposure has a high risk of harm, particularly oxidative stress and lung inflammation. Liang and his group found that in A549 cells, generation of ROS, activation of NLRP3 inflammasome, and activation of NF-κB pathway were persuaded by ZnO-NPs. The ROS scavenger NAC might prevent ZnO-NP-induced NF-κB and NLRP3 inflammasome activation. BAY11-7082, the NF-κB inhibitor, had little effect on ROS generation but reduced NLRP3 inflammasome activation produced by ZnO-NPs. The NLRP3 inflammasome was primarily responsible and was helping in regulating the production of IL-18 and IL-1β by ZnO-NPs. Hence, this can be summarised that ROS generation was induced after exposure to ZnO-NPs which further led to activate NF-κB helping in regulating the activation of inflammasomes in A549 cells.[121]

(F) Copper oxide nanoparticles. Another metal nanoparticle copper oxide nanoparticles (CuONPs) treatment triggered interleukin 1-mediated inflammation in J774A.1 macrophages for the first time *via* the NOD-, LRR-, and pyrin domain of NLRP3 inflammasome.[122,123] Tao *et al.* found that activation of NLRP3 inflammasome by CuONPs includes a two-fold process. CuONPs produced lysosomal destruction, as well as the release of cathepsin B, which facilitated the activation of NLRP3 inflammasomes directly. CuONPs may release copper ions after deposition in lysosomes, owing to the acidic environment. As a result, the free copper ions significantly increased cellular oxidative stress and facilitated NLRP3 inflammasome activation.[124]Furthermore, CuONPs exposure might stimulate J774A.1 macrophages to produce pro-IL-1β *via* the toll-like receptor 4 (TLR4) signal pathway, which is dependent on myeloid differentiation factor 88 (MyD88), consequently activating nuclear transcription factor kappa B (NF-κB) and hence affecting inflammatory pathway.[125,126]

(G) Cobalt nanoparticles. Many nanomaterials, including silver nanoparticles, amino-modified poly (phenylene glycol), and quantum dots nanoparticles, have been demonstrated in previous research to activate NLRP3 inflammation and cause the production of the inflammatory cytokine IL-1β.[103,127]

Feng and his group have used cobalt nanoparticles and revealed that nano-Co exposure to human fetal hepatocytes L02 resulted in dose- and time-dependent cytotoxicity. These nanoparticles might have caused activation of NLRP3 inflammasome in hepatocytes as they stated that the increase of NLRP3, caspase-1 p20, and IL-1β expression was seen when hepatocytes were exposed to 7.5 g mL^{-1} nano-Co for 24 hours. Nano-Co exposure at 7.5 or 10 g mL^{-1} resulted in the generation of IL-1β and IL-18.[128]

Furthermore, the Sisi group proposed that nano-Co-induced enhancement of caspase-1 p20, IL-1, and IL-18 was dramatically inhibited by NLRP3 siRNA treatment. Nano-Co-induced cytotoxicity was likewise considerably decreased by NLRP3 siRNA treatment. These findings suggested that nano-Co exposure might activate the NLRP3 inflammasome in hepatocytes, resulting in hepatocyte injury.[129]

(H) Nickel nanoparticle. Concerns concerning nickel oxide nanoparticles' (NiONPs) are increasing as manufacturing and application technology improve.[130,131] Cao and his group found that both *in vivo* and *in vitro*, NiONP exposure caused prolonged lung inflammation and NLRP3 inflammasome activation. Inflammatory cell infiltration, alveolar proteinosis, and cytokine production were all seen after NiONP exposure. The NiONPs significantly increased Nlrp3 expression, which went together with overexpression of the active form of caspase-1 (p20) and IL-1β secretion in the *in vivo* study.[132]

Furthermore, siRNA-mediated Nlrp3 knockdown in macrophages inhibited NiONP-induced release of cytokine and activity of caspase-1 proved with *in vitro* based study. Their group findings imply that the NLRP3 inflammasome participated in NiONPs-induced inflammation of the lung, and they provide novel ways to counteract NiONPs-induced pulmonary toxicity.[132]

9.1.2 Carbon based nanoparticles. Not only metal nanoparticles, carbon nanoparticles (NPs) have inflammatory properties that are hotly debated. The ability of endotoxin-free development of raw carbon nanotubes (CNTs) to stimulate inflammatory reactions *in vitro* and *in vivo* is established in the further study by the Yang group.[133–135]

Yang *et al.* proved that CNTs activate the NLRP3 inflammasome, and this property is demonstrated for the first time in carbon nano-onions (CNOs) that were spherical in the shape of 6 nm size. Purified CNTs and CNOs with benzoic acid functionalization, on the other hand, have dramatically reduced inflammatory characteristics. Following injection into mice, there was a significant reduction in the recruitment of immune cells, as well as a reduction in the release of the inflammatory cytokine IL-1β. Overall, their findings show that carbon NPs' inflammatory qualities are strongly reliant on

their physicochemical features and that chemical surface functionalization may significantly reduce these properties.[135]

9.1.3 Polymer based nanocarriers. Something hit hard with another group of people, Silke, and his group, who showed eagerness to know about the activation of NLRP3 inflammasomes by the different delivery systems. In their study, they examined other delivery carriers like lipid-based cubosomes, alum formulations, chitosan nanoparticles (CNPs) that were polymer-based, and an emulsion that is water in oil of incomplete Freund's adjuvant (IFA) that were already reported.[136–138] They examined the activation of inflammasome both *in vitro* and *in vivo*. CNPs and alum were the only positively charged particles that had the ability to activate the inflammasome and boost IL-1β production. These findings show that particle surface charge plays a role in NLRP3 inflammasome activation, which has to be taken into account when developing a new vaccine-based formulation.[139]

In contrast, a thorough examination of the nanoparticle-associated molecular patterns (NAMPs) that cause it has received little attention.[102,135] Both core and surface hydrophobicity of nanoparticles have been found to alter the permeability of the membrane and endo-lysosomal rupture (NLRP3 signal 2), which makes them promising research prospects.[140–143] Dipika *et al.* evaluated four distinct series of nanoparticles, including core stiffness, surface hydrophobicity, surface charge, and core hydrophobicity, to represent various NAMPs and their effect on NLRP3 activation. They also discovered that core hydrophobicity is a new NAMP that regulates NLRP3 activation *via* many signaling pathways, including calcium flux-mitochondrial ROS production array and lysosomal rupture-cathepsin B. In comparison to surface charge, core stiffness, and surface hydrophobicity, core hydrophobicity dramatically stimulates and positively correlates with the assembly of NLRP3 in this study.[144]

These all discussed were the latest studies that have been explored in the previous years that aid in targeting the NLRP3 inflammasome.

9.2 Drug delivery nanocarriers targeting the downregulation of signalling cascade of NLRP3 inflammasome : Protective Role

9.2.1 Metal nanoparticle targeting inflammatory cascade

(A) Zinc oxide nanoparticle. Other research contradicted the above-mentioned conclusions. The most generally found metal oxide nanoparticles are zinc oxide nanoparticles (ZnO NPs) that are broadly employed in a variety of applications due to their unique physical and chemical characteristics, which allow them to interact with cellular macromolecules and produce a variety of therapeutic effects.[145] ZnO NPs also have a variety of medicinal uses, including anti-inflammatory, bioimaging anticancer, and antibacterial. ZnO NPs have been proposed as a potential anti-diabetic drug.[146] A recent study found that giving ZnO NPs to streptozotocin (STZ) rats for six weeks relieves renal histological abnormalities, reduces renal hypertrophy and improves renal functions, as measured by creatinine clearance urine albumin, and creatinine.[147]

An existing study found that the STZ-induced DN model is well inhibited by ZnO NPs not only by monitoring advanced glycation end products and renal functions, but also by a variety of other beneficial effects such as by enhancing Nrf2-DNA-binding activity inhibiting TXNIP (thioredoxin-interacting protein) expression, which leads to suppression of oxidative stress and impeding inflammatory response by reducing activation of NLRP3.

As a consequence, ZnO NPs should be evaluated as a prospective healing agent for DN treatment.[148]

(B) Silver nanoparticles. Another study states that Jabir *et al.* revealed the green synthesis of silver nanoparticles (Ag-NPs) by using the extract of Annona muricata. Meanwhile, in both *in vivo* and *in vitro* models, the AgNPs significantly boosted autophagy and decreased IL-1β and NLRP3 levels. The IL-1β secretion was decreased, whereas the breakdown of NLRP3 inflammasome was increased. These proven data suggest that AgNPs have an anti-proliferative effect on THP-1 and AMJ-13 cell lines *via* inducing apoptosis through mitochondrial damage and activation of the p53 protein pathway. Furthermore, AgNP-induced autophagy decreased IL-1β and NLRP3 inflammasome activation.[149] Overall, this research implies that AgNPs might be a promising cancer treatment alternative to anti-inflammatory drugs by promoting autophagy and affecting the NLRP3 inflammasome activation.

9.2.2 Polymeric nanoparticles. Various polymeric and biocompatible nanoparticles also emerged as inhibitors. Andrew *et al.* discovered that a needle-like cationic derivative (cellulose nanocrystals-grafted poly-*N*-aminoethylmethacrylamide, CNC-AEMA2) elicited a robust inflammatory response in human macrophages and mice by stimulating IL-1β release. Curcumin has been shown to have antioxidant, nephroprotective, anti-ischemic, immunomodulatory, anti-inflammatory, anti-carcinogenic, anti-microbial, hepatoprotective, hypoglycemic, and antirheumatic characteristics in several scientific research studies.[150,151] The addition of curcumin to LPS induced the highest drop in NLRP3 and rose in *S*-glutathionylation of caspase-1, suggesting that protein–protein interactions are favored by curcumin in the NLRP3 complex. Our findings show that curcumin's anti-inflammatory action is linked to alterations in *S*-glutathionylation of critical components of NLRP3 inflammasome, perhaps leading to the prolonged complex formation and reduced pro-IL-1β processing and release of its active state, IL-1β.[152]

The novel finding states that an obligate Gram-negative anaerobic bacterium *Porphyromonas gingivalis* (*P. gingivalis*) was the most common bacteria in periodontal disease and has been linked to the activation of the NLRP3 inflammasome.[153] The Naip subfamily proteins of the nod-like receptor family identify the secreting and flagellin system subparts of pathogens in inflammasomes.[154] As a result, inhibiting the NLRP3 inflammasome offers a novel therapeutic technique for periodontitis treatment.[155] Ionic gelation was employed to create complex nanoparticles (CS/CMCS-NPs), including carboxymethyl chitosan (CMCS) and chitosan (CS), that form a polyelectrolyte complex which was then used as a doxycycline

carrier (Dox: CS/CMCS-NPs). Dox: CS/CMCS-NPs displayed an ordered morphology and high cytocompatibility, according to the findings. In comparison with the control group, Dox: CS/CMCS-NPs significantly suppressed *P. gingivalis*. In HGFs (human gingival fibroblasts), Dox: CS/CMCS-NPs efficiently reduced the gene and protein levels of the NLRP3 inflammasome and IL-1β. Their research offers a novel technique for using Dox in the therapeutic treatment of periodontal disease, as well as a new avenue for understanding the mechanical action of Dox: CS/CMCS-NPs and other drug-carrying based nanoparticles.[156]

Inflammatory bowel disease (IBD) is a gastrointestinal inflammatory illness that is persistent and idiopathic.[157] In all of the previously reported studies, P. Diez-Echave *et al.* postulated that silk fibroin nanoparticles would efficiently distribute quercetin to injured intestinal cells, hence increasing quercetin intestinal wound healing potential. In addition, they examine quercetin's anti-inflammatory effects in the intestine when it's loaded in silk fibroin nanoparticles in the DSS mouse colitis model.[158] The elevated expression of Nlrp3 was linked to colonic inflammation, which was considerably reduced when colitis mice were given quercetin-loaded silk fibroin nanoparticles (QSFN). Quercetin has been demonstrated to reduce NLRP3 inflammasome activation in several experimental conditions in previous *in vitro* and *in vivo* research.[159,160] However, in the current work, quercetin treatment in colitis mice only demonstrated a significant trend to the lower colonic expression of Nlrp3 when loaded in nanoparticles, suggesting that quercetin needed to be incorporated into SFN to have an anti-inflammatory impact in the intestine.[161]

9.2.3 Coordination nanoparticles. Oxidative stress causes chondrocyte death and extracellular matrix (ECM) breakdown, which contributes to osteoarthritis aetiology due to mediators like prostaglandin E2 (PGE2, matrix metalloproteinases (MMPs), and Nitric oxide, *etc*.[162,163] Curcumin which has always been extracted from *Curcuma longa* has various limitations like limited biocompatibility and low water solubility despite being an excellent antioxidant drug.[164,165] In this study, Zhou targeted to increase the water solubility of curcumin that acted as an organic ligand by conjugating it with a metal named iron and forming coordination nanoparticles.[166] The coordination nanoparticles found to be iron-curcumin-based (Fe-Cur NPs) developed to have a high-water solubility and are effective at scavenging reactive oxygen and nitrogen species (ROS/RNS). ROS/RNS that is generated intracellularly by interleukin 1 (IL-1β) could be successfully scavenged by produced Fe-Cur NPs, and further oxidative-stress induced cell death could be preserved, according to *in vitro* chondrocyte evaluation assays. In addition, Fe-Cur NPs inhibited OA progression in OA rat joints by triggering the nuclear factor-erythroid 2 related factor-2 (Nrf2) inflammasome and preventing activation of NLRP3 in primary rat chondrocytes, as well as decreasing the formation of matrix-degrading proteases and various inflammatory mediators after intra-articular (i.a.) injection. Therefore, it proves to be a promising nanoplatform for treatment in the future.[166]

9.2.4 Exosomes like nanoparticles. Not only nanoparticles but other drug delivery systems that are exosome-like nanoparticles (ELNs) or dietary exosomes have also emerged as a novel class of agents with significant translational potential.[167,168] The purpose of the Liu group was resolved as they found exosome-like nanoparticles (ELNs) that are dietary in nature and could help prevent fulminant hepatic failure (FHF) by decreasing the activation of NLRP3 that was already reported but the component of the food that depicts therapeutics potential was still a matter of concern.[169]

Seven enlisted different mushroom species were analyzed, and the author found that only shiitake mushroom-derived ELNs (S-ELNs) significantly reduced the activation of NLRP3 inflammasome by inhibiting the production of inflammasomes in primary macrophages. Protein levels of inflammatory gene IL-1β and interleukin (IL)-6 secretion were all inhibited by S-ELNs. Interestingly, mice were protected from acute liver injury by pre-treatment with S-ELNs caused by GalN/LPS. As a result, S-ELNs, which have been discovered as potent novel NLRP3 inflammasome inhibitors, constitute a promising class of medicines with the potential to treat FHF.[169]

Another interesting, relevant study elucidated that the exosome-like nanoparticles have been strongly identified from various food-borne exosome-like nanoparticles that prevent NLRP3 inflammasome activity.[170–173] From them the uniquely studied ELN to which macrophages readily absorbed is the ELNs from ginger rhizomes (G-ELNs) because it was comprised of RNAs, lipid, and proteins. G-ELN therapy inhibited autocleavage of caspase1, production of IL-18 and 1β, and pyroptotic cell death, all of which are downstream of inflammasome activation. G-ELNs inhibited NLRP3 inflammasome assembly and speck production in apoptotic speck proteins containing a caspase recruitment domain (ASC). Furthermore, It has also been found that the inhibitory action identified was due to the lipids in G-ELNs.[174] Hence, Chen and his group's findings revealed that G-ELNs are new potent inhibitors of NLRP3 inflammasome formation and activation.

9.2.5 Stimuli responsive nanoparticles. Further studies revealed that various polyphenols were found to be acting as inhibitors like Rosmarinic acid (RA), a polyphenol depicting various properties like anti-oxidant, anticancer, neuroprotective and anti-inflammatory that is metabolized in the small intestine, reducing its therapeutic benefits when taken orally.[175–177] Sonia and her group formed chitosan-coated niosomes encapsulated with RA that aid in preserving it from stomach degradation and target the colon specifically. In this study, they demonstrated that RA-loaded nanovesicles reduced IL-1 levels by downregulating protein expression of components of inflammasome that include caspase-1, NLR family pyrin domain-containing 3 (NLRP3), an adaptor protein component. Their findings show that increasing RA local bioavailability with chitosan/nutriose-coated niosomes is a potential nutraceutical method for oral colon-targeted UC treatment.[178]

Another plant-derived drug also worked as an inhibitor, as in the case of chronic kidney disease (CKD), which is marked by a progressive loss of renal function that is irreversible, further marked by a lower glomerular filtration rate. The key therapeutic objective for reducing renal injury and slowing the course of CKD is to inhibit renal inflammation.[179–181] Inflammasome activation has been linked to injury and inflammation in a variety of kidney disorders, according to previous research studies.[89,182,183] Resveratrol – loaded nanoparticles (Res NPs) coupled with an antibody named KIM-1 were employed in this study as a unique way to increase resveratrol pharmacokinetic properties, as well as its bioavailability and targetability. Resveratrol NPs may help patients with CKD by enhancing autophagy and inhibiting the NLRP3 inflammasome. Res NPs also triggered autophagy in kidney cells by boosting AMPK and hindering the Akt/mTOR signaling pathways. Kidney injury molecule-1 (KIM-1-Res NPs) improved CKD in an *in vivo* trial. These data also imply that Res NPs could be useful in treating this disease and as a possible pharmacological agent for disorders involving inflammasome.[184]

9.2.6 Prodrug based ROS responsive nanoparticle. Another different finding revealed that prodrugs could form stable nanoparticles as Sun *et al.* devised an activatable, targeted nanosystem that is ROS based on helping in detecting and visualizing immune-inflammatory disorders (CAR-induced hind paw edema and ConA-induced autoimmune hepatitis), as well as treating these diseases by blocking the NF-κB signaling pathway and decreasing NLRP3 activity. A prodrug named BH-EGCG that is activated by the ROS environment is produced through the boronate bond, which functions as both a fluorescence-based quencher and the ROS-responsive moiety, and is used to link a near-infrared chromophore with the NF-κB/NLRP3 inhibitor named epigallocatechin-3-gallate (EGCG).[185–187] In aqueous media, BHEGCG molecules easily form stable nanoparticles, which are subsequently coated with the membrane of the macrophage to ensure active targeting of inflammatory sites. Using the macrophage membrane's inflammation-homing effect, the nanosystem more efficiently delivers payloads to inflammatory lesions, resulting in improved theranostic performance and therapeutic efficacy by reducing the NF-κB pathway and inhibiting NLRP3 inflammasome activation.

The newest and most interesting inhibitor of NLRP3 inflammasome is dopamine which also acts as curing therapy for liver disease.[188] Inflammasome, a newly discovered and intriguing target for successful therapy of immunity-associated disorders such as liver disease.[189] This study shows that a diselenide-based nanodrug can be used to treat ALF (acute liver failure) by suppressing the NLRP3 inflammasome and improving liver regeneration. In conclusion, Zhan and his group developed a diselenide-based nanosystem that has been synthesized by linking two dopa molecules by the covalent bond that results in stable nanoparticles when seen in aqueous media for the treatment of ALF, which is the first attempt to use a nano-prodrug generated by molecular diselenide in the treatment of liver disease. This method can not only prevent additional liver injury by suppressing the production of the NLRP3 inflammasome but also accelerate liver regeneration by downregulating 15-PGDH (prostaglandin-degrading enzyme 15), resulting in enhanced therapeutic effectiveness for ALF.[190]

9.2.7 Liposomal drug delivery system. Another study related to IBD depicts that Patchouli alcohol, the main active compound in the Chinese herb patchouli, was converted into biomimetic liposomes for macrophage-based targeted delivery in the treatment of IBD in this work.[191,192] Lactoferrin-modified liposomes (LF-lipo) have been produced that can specifically bind to LRP-1 expressed on activated macrophages of the colon, allowing for cell-targeting anti-inflammatory treatment. LF-lipo inhibited the MAPK/NF-κB pathway and lowered the levels of inflammatory cytokines and ROS. LF-lipo also inhibited the development of the NLRP3 inflammasome and the subsequent activation of IL-1b.[193]

9.2.8 Nanomicelles drug delivery system. In 2022, Lihe Sun *et al.* developed an orally administered nanocarrier system tar-

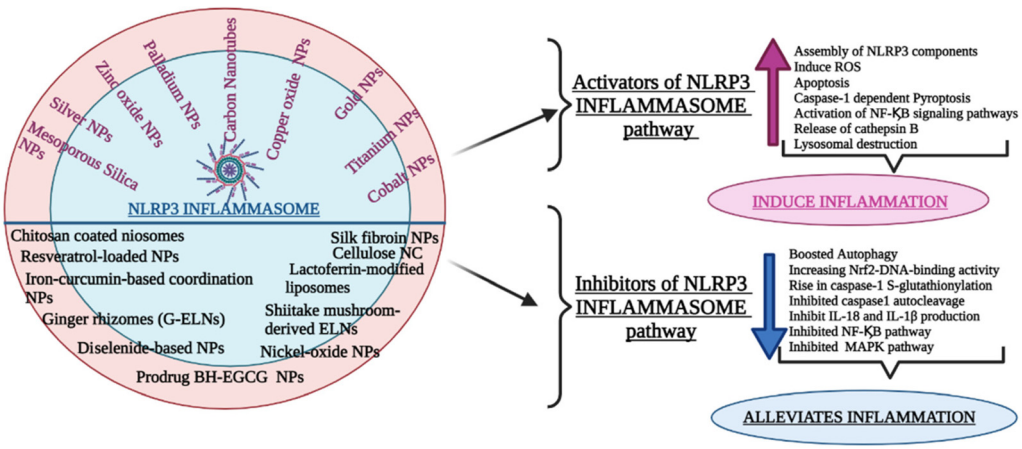

Fig. 6 Schematic representation of various metal and polymer-based drug deliver carriers including nanoparticles, liposomes and exosomes for targeting the NLRP3 inflammasome pathway and hence curing various inflammatory diseases.

Table 1 The therapeutic effects of different drug delivery carriers targeting inflammation *via* the NLRP3 inflammasome

Delivery carrier	Signalling pathway	*In vivo* and *in vitro* studies	Activation/ inhibition	Ref.
Silver and palladium NPs	Decrease cathepsin B expression and the quantity of acidic organelles *via* lysosomal injury	Human oral keratinocytes	Activation of NLRP3	88
Gold NPs	Ultrasmall Au nanoparticles – robust ROS production and targeting autophagy protein-LC3 for proteasomal degradation in an endocytic/phagocytic-independent manner	Mouse bone marrow-derived dendritic cells	Activation of NLRP3	97
Titanium dioxide NPs	Cause assembly of NLRP3-ASC-caspase-1, caspase-1 cleavage, and the release of NLRP3-associated interleukin (IL)-1β and IL-18	*In vitro*: human intestinal epithelial cells and macrophages *In vivo*-acute colitis	Activation of NLRP3	99
Nano-TiO_2 and nano-SiO_2NPs	P2Y1, P2Y2, A2A, or A2B receptor expression in NLRP3 increased *via* activating PLC-InsP3 and/or inhibiting adenylate cyclase (ADCY)-cAMP pathways	*In vitro*: murine bone-marrow-derived macrophages	Activation of NLRP3	103
Titanium dioxide NPs	Induce ROS, apoptosis, caspase-1 activation, and inflammation	*In vivo*: liver and intestinal disorders	Activation of NLRP3	105
Silica NPs	Stimulate the production of inflammasome components (NLRP3, ASC, Casp-1), as well as IL-1b, IL-6, and IL-18	PBMC and neutrophils in a dose dependent manner	Activation of NLRP3	107
Silica NPs	Produce excessive ROS that activate the NLRP3 inflammasome *via* TLR4/MyD88/NF-κB signaling pathways, and speed up the lysine acetylation of HMGB1	Human umbilical vein endothelial cells (HUVECs)	Activation of NLRP3	108
Mesoporous silica nanoparticles (MSNs)	Activation of NLRP receptor by excessive production of ROS and leading to caspase-1-dependent pyroptosis	Hepatic L02 cell and liver inflammation	Activation of NLRP3	112
Zinc-oxide NPs	Generation of ROS, activation of the NLRP3 inflammasome *via* activation of the NF-κB pathway	A549 cells	Activation of NLRP3	121
Copper oxide NPs	Liberated copper ions, increase oxidative stress, lysosomal destruction, release of cathepsin B, and activation of NLRP3 *via* MyD88 and NF-κB pathways	J774A.1 macrophages	Activation of NLRP3	124
Cobalt NPs	Increase of NLRP3, caspase-1 p20, and IL-1β expression	Human fetal hepatocytes L02	Activation of NLRP3	128
Silver NPs	Cause autophagy and permeabilization of the lysosomal membrane, resulting in caspase-1 activation *via* the NLRP3 inflammasomes	HepG2 cells	Activation of NLRP3	107
Nickel-oxide NPs	Increase NLRP3 expression, overexpression of the active form of caspase-1 (p20), and IL-1β secretion	*In vivo*: lung inflammatory model	Activation of NLRP3	132
Chitosan NPs	Cathepsin B mediated activation of NLRP3 *via* the lysosomal rupture activation process	*In vitro*: murine BMDCs *In vivo*: peritoneal macrophages and *in vitro*	Activation of NLRP3	139
Zinc oxide NPs	Increasing Nrf2-DNA-binding activity and downregulating TXNIP gene expression, which leads to oxidative stress suppression and inhibiting the inflammatory response by attenuating NLRP3 inflammasome activation	STZ-induced DN model	Inhibition of NLRP3	148
Silver NPs	Boosted autophagy and decreased IL-1β and NLRP3 levels *via* promoting autophagy	THP-1 and AMJ-13 cells lines	Inhibition of NLRP3	149
Cellulose nanocrystals-grafted poly-*N*-aminoethylmethacrylamide	The highest drop in NLRP3 and rise in caspase-1 *S*-glutathionylation, prolonged complex formation, and reduced pro-IL-1β processing and release of its active state	Mouse macrophage-like cells J774A.1	Inhibition of NLRP3	152
CS/CMCS-NPs	Reduced protein levels of the NLRP3 inflammasome and IL-1β	Primary human gingival fibroblast cell line	Inhibition of NLRP3	156
Iron-curcumin-based coordination NPs	Activating the nuclear factor erythroid 2 related factor-2 (Nrf2) and inhibiting nod-like receptor protein-3 (NLRP3) inflammasome activation	*In vivo*: rat osteoarthritis model	Inhibition of NLRP3	166
Shiitake mushroom-derived ELNs (S-ELNs)	Inhibit the production of inflammasomes, interleukin IL-6 secretion, and protein and mRNA levels of IL-1β	Fulminant hepatic failure primary macrophages	Inhibition of NLRP3	169
Ginger rhizomes (G-ELNs)	Inhibited caspase1 autocleavage, interleukin (IL)-1 and IL-18 production, and pyroptotic cell death, all of which are downstream of inflammasome activation	Bone marrow-derived macrophages (BMDMs) from C57BL/6J mice	Inhibition of NLRP3	174

Table 1 *(Contd.)*

Delivery carrier	Signalling pathway	*In vivo* and *in vitro* studies	Activation/ inhibition	Ref.
Chitosan coated niosomes	Reduced IL-1β levels by downregulating protein expression of components of the inflammasome that include caspase-1, NLRP3, and adaptor protein components	*In vivo*: DSS-induced colitis model	Inhibition of NLRP3	159
Resveratrol-loaded nanoparticles (Res NPs) coupled with KIM-1 antibody	Triggered autophagy in kidney cells by boosting AMPK and inhibiting the Akt/mTOR signaling pathway	*In vivo*: chronic kidney disease mouse model *In vitro*: HK-2 cell line	Inhibition of NLRP3	184
Prodrug BH-EGCG NPs	Inhibiting the NF-κB pathway and suppressing NLRP3 inflammasome activation	CAR-induced hind paw edema and ConA-induced autoimmune hepatitis mouse models	Inhibition of NLRP3	157
Silk fibroin NPs	Lower the colonic expression of Nlrp3 when loaded in nanoparticles	*In vivo*: DSS mouse colitis model	Inhibition of NLRP3	161
Lactoferrin-modified liposomes	Inhibited the MAPK/NF-κB pathway and lowered the levels of inflammatory cytokines and ROS	*In vitro*: colonic macrophages	Inhibition of NLRP3	193
Diselenide-based nanodrug	Suppressing the production of the NLRP3 inflammasome but accelerating liver regeneration by downregulating 15-PGDH	*In vitro*: NCTC-1469 cells *In vivo*: ALF mouse model	Inhibition of NLRP3	190

geting ulcerative colitis (UC). The nanosystem integrated a molecular probe for UC detection, encapsulating the NLRP3 inhibitor MCC950. A controlled release was facilitated by coating with Eudragit S100, triggered by colonic pH. The released drug exhibited potent therapeutic efficacy by hindering NLRP3 assembly formation, effectively attenuating ulcerative colitis progression.[194]

In 2023, Ravi *et al.* and their team developed pH-responsive nanomicelles for ischemic stroke therapy. They incorporated MCC950, an NLRP3 inhibitor, into transferrin-conjugated nanomicelles to facilitate blood–brain barrier penetration. The study demonstrated that nanomicelle treatment notably reduces NLRP3 inflammasome biomarker levels, which were elevated in the right vitelline artery (RVA) of I/R-induced chick embryos, the MCAO rat model, and oxygen-glucose deprived (OGD) SH-SY5Y cells. A key finding is the significant mitigation of oxidative and inflammatory stress through pharmacological NLRP3 suppression by MCC950, observed in *in vitro*, *in ovo*, and *in vivo* contexts.[195]

(A) Top of form. Therefore, all the above-cited group of studies gives an overview of the interplay between NLRP3 inflammasome and various other nanoparticles affecting its mechanism of signaling and elucidating their potential as therapeutic targets. Fig. 6 provides a comprehensive overview of diverse drug delivery carriers employed for targeting the inflammatory pathway within different disease models *via* the NLRP3 signaling pathway.

10. Conclusion and future perspectives

Inflammasome biology has advanced rapidly in recent years, surpassing the fundamental notion established in the early 2000s. The molecular basis of ligand recognition has been discovered for numerous receptors. The finding and characterization of the non-canonical inflammasome pathway and pyrin inflammasome have generated new paradigms for how the innate immune system recognizes microbial invaders.[196] In addition, numerous vital actors that influence downstream signaling have been discovered to affect the molecular processes that drive the oligomerization of receptors, complex building, and signal propagation within that complex. As a critical node for immunological detection within the innate immune system, NLRP3 activation or inhibition may be therapeutically valuable in some cases. Abnormal NLRP3 activation is at the root of the harmful inflammation that underpins many degenerative diseases linked to ageing and lifestyle. Small compounds that suppress NLRP3 activation have been shown to reduce inflammasome signaling in mouse models of different inflammatory illnesses in recent research (Table 1). The novel approaches that outlined the various nanoparticle targeting strategies emphasized in this review provide a road map for creating targeted therapies by altering inflammasome signaling. This might pave the way for inflammasome signaling targeting in specified inflammatory illnesses.

Author contributions

Dr Rehan Khan conceived the idea and the outline of this manuscript and edited it. Kanika wrote the manuscript, drew the figures, organized the table and revised the manuscript.

Abbreviations

NLRP3	NOD-, LRR- and pyrin domain-containing 3
IL-1β	Interleukin-1β
TLRs	Toll-like receptors
CTLs	C-type lectins
NLRs	Nod like receptors
PRRs	Pattern recognition receptors

AIM2	Absent in melanoma 2
CARD	Caspase recruitment domain
PYDs	Pyrin domain
LRRs	leucine-rich repeats
ASC	Associated speck-like protein
LPS	Lipopolysaccharide
PAMPs	Pathogen-associated molecular patterns
DAMPs	Danger-associated molecular patterns
IL-18	Interleukin IL-18
ATP	Adenosine triphosphate
NEK7	Serine/threonine-protein kinase
ROS	Reactive oxygen species
mtROS	Mitochondrial ROS
IBD	Inflammatory bowel disease
MtD	Mitochondrial dysfunction
NO	Nitric oxide
mtDNA	Mitochondrial DNA
ATG16L	Autophagy related protein 16 L
CRC	Colorectal cancer
HFD	High fat diet
CAPS	Cryopyrin-associated periodic fever syndrome
DSS	Dextran sulfate sodium
DCs	Dendritic cells
Au	Gold
LC3	Light chain 3
IECs	Intestinal epithelial cells
TiO_2	Titanium dioxide
Ag-NPs	Silver nanoparticles
MSNs	Mesoporous silica nanoparticles
CuONPs	Copper oxide nanoparticles
MyD88	Myeloid differentiation factor 88
NF-κB	Nuclear transcription factor kappa B
ADP	Adenosine diphosphate
SiO_2	Silica dioxide
ADC	Adenylate cyclase
ALF	Acute liver failure
15-PGDH	Prostaglandin-degrading enzyme 15
SiNPs	Silica nanoparticles
HUVECs	Human umbilical vein endothelial cells
HMGB1	High-mobility group box 1
P. gingivalis	*Porphyromonas gingivalis*
CS	Chitosan
CMCS	Carboxymethyl chitosan
Dox: CS	Doxycycline carrier
HGHs	Human gingival fibroblasts
CNOs	Carbon nano-onions
CNTs	Carbon nanotubes
ZnO NPs	Zinc oxide nanoparticles
STZ	Streptozotocin
AGEs	Advanced glycation end products
DN	Diabetic nephropathy
TXNIP	Thioredoxin-interacting protein
CNPs	Chitosan nanoparticles
IFA	Incomplete Freund's adjuvant
NiONPs	Nickel oxide nanoparticles
OVA	Ovalbumin
BMDCs	Bone marrow-derived dendritic cells
NS	Non-sensitized mice
RA	Rosmarinic acid
HO-1	Heme oxygenase-1
ELNs	Exosome-like nanoparticles
S-ELNs	Shiitake mushroom-derived ELNs
FHF	Fulminant hepatic failure
EGCG	Epigallocatechin-3-gallate
CNCs	Cellulose nanocrystals
ECM	Extracellular matrix
PGE2	Prostaglandin E2
MMPs	Matrix metalloproteinases
Fe-Cur NPs	Iron-curcumin-based coordination nanoparticles
Nrf2	Nuclear factor-erythroid 2 related factor-2
CKD	Chronic kidney disease
IBD	Inflammatory bowel disease
QSFN	Quercetin silk-fibroin nanoparticle
LF-Lipo	Lactoferrin-modified liposomes
NAMPs	Nanoparticle-associated molecular patterns
CNC-AEMA2	Cellulose nanocrystal-grafted poly-*N*-aminoethylmethacrylamide
CH-Al NPs	Chitosan-aluminum nanoparticles

Conflicts of interest

The authors declare that there are no conflicts of interest.

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