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Review

Pharmacological Modulation of NLRP3: From Therapy Personalization to Innovative Drugs

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Abstract

The nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome is a multiprotein complex fundamental for the secretion of pro-inflammatory cytokines during the innate immune response. NLRP3 dysregulation is implicated in the pathogenesis of several diseases, such as inflammatory bowel disease, arthritis, cancer, Alzheimer's disease, and type 2 diabetes. The pharmacological modulation of NLRP3 by several compounds, which are fully described in this review, represents an important strategy to regulate inflammatory processes. Moreover, NLRP3 is also involved in drug-related adverse reactions, and its pharmacological modulation represents a rapid strategy to mitigate such adverse effects, as reported in this study. NLRP3 inflammasome activation is tightly regulated by post-transcriptional modifications and epigenetic factors, such as long non-coding RNAs (lncRNAs) and DNA methylation, as well as other interacting regulators. Recently, different studies have revealed the importance of NLRP3 levels in predicting drug response. In particular, the methylation of the NLRP3 promoter, which is associated with the inflammasome expression level, emerged as a new promising pharmacoepigenetic biomarker for the glucocorticoid therapy response in several inflammatory disease conditions.

Keywords: NLRP3; inflammasome; personalization therapy; biomarker

1. Introduction

The human immune system comprises both adaptive immunity and innate immunity, with the latter serving as the first line of defense [1]. Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasomes are intracellular multimeric protein complexes that activate pro-caspase-1, which is crucial for the initiation and control of inflammation. This activation is fundamental for the innate immune system activation and consequent inflammatory modulation. Notably, inflammasome dysregulation has been found to be involved in different inflammatory chronic conditions, including rheumatoid arthritis, systemic lupus erythematosus, type 2 diabetes, atherosclerosis, ischemic heart disease, liver diseases, amyotrophic lateral sclerosis, inflammatory bowel disease (IBD), Parkinson's and Alzheimer's disease [2]. Given that NLRP3 activity is tightly regulated, different pharmacological approaches have been developed to identify molecules capable of modulating its activity, thereby leading to inflammatory regulation.

The NLRP3 inflammasome formation, activation and modulation are straightly related to the immune response activation and maintenance. In particular, the innate immune response recognizes different pathogen-associated molecular patterns (PAMPs, e.g., bacterial products like lipopolysaccharides) and derived danger-associated molecular patterns (host DAMPs, e.g., uric acid crystals, adenosine triphosphate (ATP)) through the pattern recognition receptors (PRRs) to activate a physiological response against pathogens [3]. These PRRs subsequently oligomerize to form inflammasomes [4], whose caspase-1-mediated activation stimulates the secretion of proinflammatory cytokines, such as interleukin (IL)-1β and IL-18 [5]. Nowadays, five members of PRRs have been identified: Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), retinoic acid-inducible gene I-like receptors (RLRs), C-type lectin receptors (CLRs), and absent in melanoma 2-like receptors (ALRs). These receptors are able to generate inflammasome complexes, which include nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing proteins (NLR) family members (NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, NLRP12 and NLRC4), IFI16, AIM2 and pyrin. The inflammasomes are formed by the combination of NLRP complex, pro-caspase1 and the apoptosis-associated speck-like protein (ASC) complex, which contains a caspase-recruitment domain (Fig. 1) [4]. The distinct NLRP isoforms play specialized functions, present tissue-specific expression patterns, and are activated in response

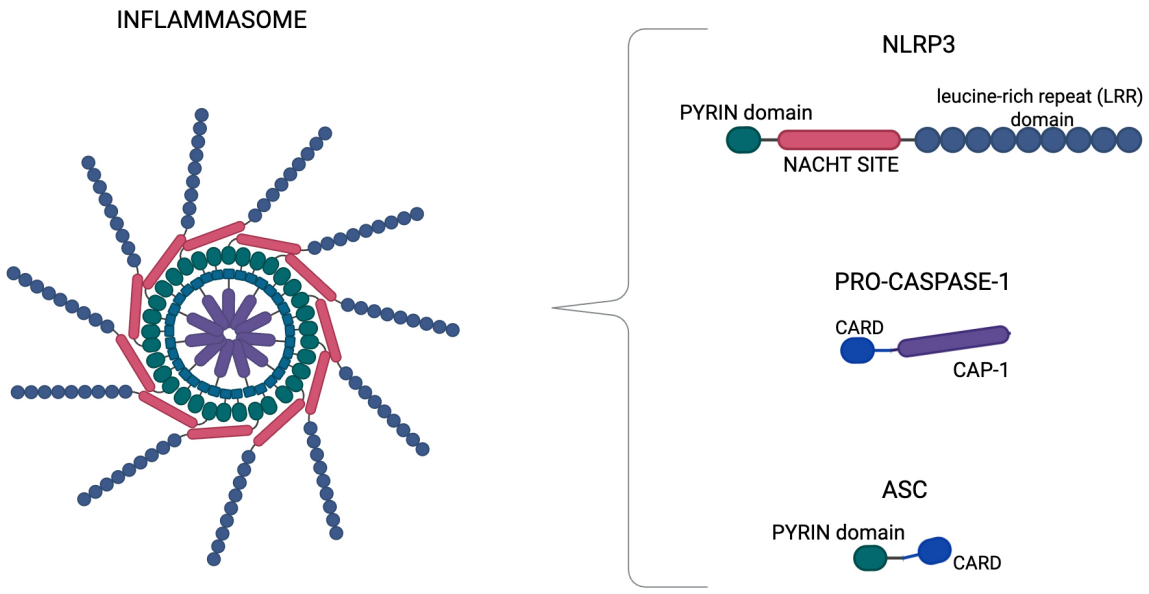

Fig. 1. Inflammasome structure. Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome structure, which is a complex composed by NLRP3, apoptosis-associated speck-like protein (ASC), and procaspase-1. NLRP3 shows three regions: the pyrin domain in the amino terminus, the NACHT site, and the LRR (leucine-rich repeat) domain in the carboxy terminus. NLRP3 recruits ASCs through pyrin-pyrin domain interactions. In turn, procaspase-1 is recruited by ASC through Caspase Recruitment Domain (CARD)-CARD interactions to form the NLRP3-ASC-procaspase-1 (CAP-1) inflammasome. In particular, we generated Figs. 1,2 using BioRender.com (BioRender Inc., Toronto, Canada).

to different processes [4]. For instance, NLRP1, NLRP3 and NLRP12 are expressed in various immune cells involved in inflammatory responses, such as macrophages, dendritic cells, and neutrophils, whereas NLRP6 is primarily expressed in the gastrointestinal tract, particularly in the colon, where it is involved in intestinal homeostasis maintenance [6]. Furthermore, the activation of NLRP1 can be stimulated by bacterial toxins [7], and recent studies have reported that NLRP12 modulates immune responses against viral [8] or parasitic infections [9]; however the NLRP12 activation is less characterized compared to NLRP1 and NLRP3.

Since NLRP3 is the best characterized and studied isoform, this review focuses on NLRP3 description. As previously specified for all inflammasome classes, NLRP3 can be activated by several stimuli, including PAMPs and DAMPs to form an inflammasome that activates caspase-1 and promotes the maturation and secretion of IL-1β and IL-18 [10]. The molecular mechanism underlying its activation and modulation will be deeply discussed in the following sections.

2. The Mechanism of NLRP3 Activation

NLRP3 activation is finely regulated, depends on different factors, and comprises several steps. This complex mechanism is divided into two main phases: the priming step and the activation step [10,11]. The priming step consists of increased cellular expression levels of pro-IL-1β, pro-IL-18 and NLRP3 transcripts following TLRs and nuclear factor-κB (NF-κB) activation. The activation phase induces NLRP3 inflammasome oligomerization, leading to the recruitment of ASC and pro-caspase-1, which are responsible for the release of inflammatory cytokines IL-1β and IL-18, the main drivers of phlogosis.

In cells, NLRP3 activation can be induced by different stimuli, such as the K^+ and Cl^- efflux due to PAMPs/DAMPs [12,13], Ca^{2+} release from endoplasmic reticulum [14], intracellular accumulation of reactive oxygen species (ROS) [15], mitochondrial dysfunction [16], the presence of metabolic changes, trans-Golgi disassembly [17], and lysosomal disruption due to particulate matter accumulation, such as alum, silica, asbestos, amyloid-β and cholesterol crystals [4,18]. However, Katsnelson *et al.* [19] demonstrated that higher levels of lysosomal membrane disruption, due to cellular stress conditions, increased K^+ cellular efflux and higher Ca^{2+} release from endoplasmic reticulum, lead to inflammasome signaling suppression. Similarly, NLRP3 inflammasome inhibition was obtained after treatment with inhibitors of TLR4, NF-κB and other molecules used to reduce inflammation in different inflammatory pathological conditions, such as atherosclerosis, ischemic stroke, Alzheimer's disease, diabetes mellitus and IBD [20]. Indeed, several cellular, genetic and epigenetic mechanisms corroborate to modulate NLRP3 activ-

ity, and their possible dysfunction may be involved in the pathological development of disease conditions, as deeply explored in the next paragraphs.

3. The Fine Regulation of NLRP3 Activation

It is important to consider that NLRP3 interacts with different regulatory proteins. Many proteins, such as chaperone heat shock protein 90 (Hsp90) and its co-chaperone the suppressor of G2 allele of Skp1 (SGT1), are important for NLRP3 conformation and stability [21]. Additionally, Thioredoxin-Interacting Protein (TXNIP) serves as an oxidative sensor and interacts with thioredoxin (TRX) under reducing conditions; in the presence of ROS, TRX dissociates from TXNIP, permitting its interaction with NLRP3 and leading to inflammasome activation [22]. Moreover, guanylate-binding protein 5 (GBP5) binds to the pyrin domain of NLRP3, promoting ASC oligomerization and facilitating inflammasome activation [23]. Other factors, such as the double-stranded RNA-dependent protein kinase (PKR), migration inhibitory factor (MIF) and microtubule-affinity regulating kinase 4 (MARK4), are able to interact with NLRP3, leading to its inhibition or activation through a variety of mechanisms that involve stress sensing, autophagy, and proteasomal degradation [24,25]. Together, these findings underscore the importance of correct NLRP3 functionality, which is involved in several cellular mechanisms responsible for intracellular degradation of exogenous stress sources, such as pathogens, and demonstrate that disruptions in these systems can contribute to tissue inflammation.

From a molecular point of view, different post-transduction modifications, such as phosphorylation, ubiquitination and SUMOylation, are involved in NLRP3 inflammasome activation and modulation, as detailed below.

NLRP3 inflammasome can be phosphorylated during both the priming phase and the activation phase, and phosphorylation can also be involved in the inflammasome regulation during inflammatory resolution [26]. Phosphorylation at different sites of NLRP3 inflammasome is responsible for its activation, and several kinases are involved in these mechanisms, including TGF-β-activated kinase 1 (TAK1), the mitogen-activated protein kinase kinase kinase (MAPKKK) family, such as JNK1, the p21-activated kinase (PAK) family proteins, the protein kinase A (PKA) and the protein kinase D (PKD) [27]. Song *et al.* [28] demonstrated that JNK1-mediated NLRP3 phosphorylation at the Ser194 residue during the priming phase is essential for NLRP3 assembly and activation, and other evidences showed that the pyrin domain of NLRP3 is crucial for its activation by phosphorylation [29]. Also kinases of the inhibitor of κB kinases (IKKs) family, through phosphorylation of NLRP3 have a crucial role for the modulation of inflammasome activation [28]. Also NLRP3 ubiquitination, has a role in inflammasome activation and autoinhibition [30]. Indeed, it was demonstrated that both F-box/LRR-repeat protein 2 (FBXL2) and Parkin RBR E3 ubiquitin protein ligase 2 (PARK2) mediate NLRP3 ubiquitination, inhibiting inflammasome activation and facilitating NLRP3 proteasomal degradation [31,32]. The ubiquitination may be also responsible for NLRP3 intracellular translocation. In particular, the E3 ubiquitin ligase gp78 [33], the E3 Ubiquitin Ligase Tripartite Motif-containing protein 65 (TRIM65) [34] and the E3 ligase Ariadne homolog 2 (ARIH2) [35] ubiquitinate and inhibit NLRP3, suppressing its oligomerization and subcellular translocation. These evidences highlight that modulation of NLRP3 ubiquitination may be considered a new possible target for anti-inflammatory therapeutic approaches [36].

In recent years, also SUMOylation emerged as an important post-translational modification of inflammasome. NLRP3 SUMOylation at multiple sites occurs by the E3 SUMO protein ligase MUL1 (MAPL) and regulates NLRP3 activation; in particular, it has been found that upon activation, NLRP3 becomes deSUMOylated by sentrin-specific protease 6 (SENP6) and SENP7, and defects in the SUMOylating mechanisms may lead to NLRP3 hyperactivation [37].

4. The Role of Epigenetic Factors in the Modulation of NLRP3

Since epigenetic factors, such as microRNAs and long non-coding RNA (lncRNA), have recently been recognized as crucial regulators of NLRP3 inflammasome by targeting NLRP3 mRNA [38], this section reports the epigenetic mechanisms identified as involved in NLRP3 regulation.

Among the various microRNAs implicated in NLRP3 modulation, several have been extensively characterized for their regulatory roles. For instance, a study has demonstrated that miR-9 inhibits NLRP3 inflammasome in cardiomyocytes, leading to cardiac cell death and heart failure [39]. In contrast, miR-223 inhibits NLRP3 inflammasome, resulting in reduced myocardial damage in both *in vitro* and *in vivo* models, while miR-22 acts as negative regulator of NLRP3 during tumorigenesis [40]. Similarly, miR-21 has been identified as a regulator of inflammasome activation through direct interaction with NLRP3 mRNA [41]. However, miR-21 also exerts indirect effects on NLRP3 regulation. Specifically, miR-21 targets and downregulates Phosphatase and tensin homolog (PTEN) [42], which in turn negatively regulates AKT1, a kinase responsible for NLRP3 phosphorylation [28]. This regulatory cascade suggests a complex indirect mechanism by which miR-21 influences inflammasome activity. Furthermore, Scalavino *et al.* [43] demonstrated that miR-369-3p reduces the expression of BRCA1/BRCA2-containing complex 3 (BRCC3), a key regulator of NLRP3 activation through de-ubiquitination [44]. By targeting BRCC3, this miRNA blocks the recruitment of ASC adaptor to the inflammasome complex, ultimately reducing NLRP3 activity.

In addition to miRNAs, several lncRNAs have emerged as crucial inflammasome regulators, modulating NLRP3 at both transcriptional and post-transcriptional level. A prominent example is Nuclear Enriched Abundant Transcript 1 (NEAT1), a lncRNA [45] normally located in the nucleus, where it is responsible for the maintenance of the structural integrity of the paraspeckles in the chromatin by associating with nuclear RNA binding proteins [46]. Upon stimulation with inflammasome-activating signals, NEAT1 disassociates from paraspeckles proteins and migrates into the cytoplasm, where it promotes inflammasome activation by facilitating the assembly of NLRP3, NLRC4 and AIM2. This occurs through NEAT1's ability to bind and stabilize mature caspase-1 tetramers, increasing their protease activity [45]. Supporting this mechanism, an *in vivo* study performed on allergic rhinitis models demonstrated that NEAT1 can trigger NLRP3-mediated pyroptosis through activation of the PTBP1/FOXP1 signaling cascade [47].

Another important lncRNA in NLRP3 regulation is metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). Elevated MALAT1 levels have been consistently associated with higher NLRP3 activation and consequent increased inflammation across different pathologies, including Parkinson's disease [48], myocardial infarction [49], diabetes and atherosclerosis [50–52]. Mechanistically, MALAT1 plays a key role in the NLRP3-mediated pyroptosis in conditions such as osteoarthritis [53] and colitis [54] through its ability to modulate specific miRNAs, that regulate NLRP3 expression and activity, such as miR-124-3p [53] and miR-22-3p [54].

Together, these evidence highlight the role of NLRP3 epigenetic regulation and the disruption of these mechanisms may be involved in chronic inflammatory disorders and cancer conditions, underlining the importance of a tight and functional inflammasome regulation.

5. Pharmacological Modulators of NLRP3 as Therapeutic Approaches for Inflammatory Regulation

Since NLRP3 inflammasome is crucial in the modulation of phlogosis and consequently in different physiological processes several NLRP3 pharmacological modulators have been identified (**Supplementary Fig. 1**), which could play a role in inflammatory chronic disease treatment [55].

In neurodegenerative diseases, such as Parkinson's disease, glibenclamide has shown a neuroprotective effect on dopaminergic neurons, through the reduction of over-regulated α-synuclein, a component of Lewy bodies, reducing NLRP3 activation and the production of IL-1β [56]. NLRP3 inflammasome influences some central nervous system diseases, such as major depressive disorder, which are mainly treated with common antidepressant drugs, such as fluoxetine. This drug, which is a selective serotonin reuptake inhibitor, has also been shown to inhibit NLRP3 and caspase-1 activity and consequently the expression of IL-1β and IL-18 inflammatory cytokines in microglia. In particular, the inhibitory effect of fluoxetine on NLRP3 inflammasome occurs by inhibiting the ROS-double-stranded RNA-dependent protein kinase (PKR)-NLRP3 signaling pathway in peripheral macrophages and central microglia [57]. Additionally, different NLRP3 inhibitors, such as selnoflast, usnoflast (also called ZYIL1) [58], DFV890 [59] and NT-0796 [60], are being investigated in clinical trials for neurological and cardiovascular disease conditions [61]. Colchicine, a drug widely used in different inflammatory disorders (e.g., coronary diseases, gout, pericarditis, familial Mediterranean fever), is able to reduce the activation of NLRP3 inflammasome [62]. In acute coronary syndrome, the colchicine inhibitory action is exerted by decreasing pro-caspase-1 mRNA synthesis and caspase-1 protein levels, which is probably due to the drug's immunomodulatory action, leading to the arrest of pro-IL-1β cleavage and secretion of active IL-1β, as shown in a group of 21 acute coronary syndrome adult patients who were randomized to oral colchicine or no treatment, and compared with untreated healthy controls [63]. A randomized clinical trial showed the inhibitory effect of colchicine on the NLRP3 inflammasome in 72 adult patients with COVID-19 infection presenting systemic inflammation and needing supplemental oxygen, although now it is not recommended for the management of SARS-CoV-2 infections. An analysis of the patients serum showed that subjects treated with colchicine presented lower values of caspase-1 and IL-18, which were associated with the drug inhibitory effect on NLRP3 inflammatory activity [64]. Among the pharmacological inhibitors of NLRP3, there is also tranilast, an anti-allergic drug widely used in Asian countries for its safe profile, even at high doses [65]. This molecule is an anthranilic acid analog responsible for Vascular Endothelial Growth Factor (VEGF) inhibition and consequent blockade of IgE-induced histamine release from mast cells [66]. Importantly, Huang *et al.* [67] demonstrated that this tryptophan metabolite analog can also inhibit NLRP3 inflammasome in macrophages, through binding to a specific NLRP3 inflammasome domain, called the NACHT site, thereby blocking NLRP3 oligomerization capacity. Similarly, the non-steroidal anti-inflammatory drug fenamate (mefenamic acid) inhibits NLRP3 both *in vivo* and *in vitro* through blocking of Cl^- volume-regulated anion channels (VRAC), affecting the Cl^- and K^+ ion fluxes, which are crucial for NLRP3 activation, and ultimately reducing brain inflammation and memory deficit in Alzheimer's disease animal models [68]. Recently, different new molecules have been tested and found to be promising NLRP3 inflammasome inhibitors. Among these, MCC950 or CP-456773, is a diaryl sulfonylurea that is a selective inhibitor of NLRP3 thanks to its ability to bind the NACHT site, thereby interfering with the NLRP3 binding capacity for adenosine diphosphate (ADP)/ATP, reducing its ATPase activity, and lead-

ing to lower maturation and release of IL-1β [69,70]. Several preclinical studies have demonstrated MCC950 possible application in different inflammatory chronic diseases, such as asthma [71], atherosclerosis [72] and influenza A viral infection [73], on *in vitro* and *in vivo* models on the basis of its ability to reduce inflammasome activation and decreasing the secretion of pro-inflammatory cytokines, such as IL-18, IL-1β and IL-1α. Moreover, it was proved that MCC950 can show a neuronal protective effect in a mouse model of traumatic brain injury [74] and in diabetic rats after stroke [75]. Evidence demonstrated that MCC950 enhanced also the blood brain barrier and vascular integrity by reducing the endothelial NLRP3 expression [76]. In a study investigating the activity of MCC950 in porcine myocardial infarction models, a dose-dependent reduction of intra-myocardial IL-1β was shown, leading to lower size of the infarction site and preservation of the cardiac function [77]. In rheumatoid arthritis, pharmacological inhibition of MCC950-mediated NLRP3 inflammasome could also provide new therapeutic strategies; however, a small clinical study showed an increased risk of MCC950-related hepatotoxicity, leading to the discontinuation of the study [78]. Both *in vitro* and *in vivo* evidence demonstrated that fadraciclib (also known as CY-09) is a small benzothiazole-derived molecule presenting specific inhibitory activity against NLRP3 through its ability to bind the NLRP3 inflammasome NACHT domain, preventing its oligomerization and consequent inflammatory activation [70]. In a study on hepatic steatosis in mice, CY-09 showed also a promising activity on the reduction of insulin resistance and weight gain [79]. CY-09 can be also used for the treatment of different NLRP3-correlated diseases, like gout, where it was associated with a dose-dependent reduction of IL-1β and caspase-1 levels [80], diabetic nephropathy, where it seemed to protect kidney from hyperglycemia damage [81] and thrombosis, where CY-09 therapy lowered platelet aggregation on *in vivo* models [82]. A recent *in vivo* study showed that the benzoxazolone acetamide analogue C77 inhibited NLRP3 through the binding of the NACHT domain in brain regions, such as cortex, front cortex, hippocampus, and cerebellum of mice presenting neurodegenerative disease [83]. Both *in vitro* and *in vivo* studies identify dapansutrile (also known as OLT1177), a β-sulfonylnitrile compound, as a specific inhibitor of NLRP3 inflammasome thanks to its ability to block ASC recruitment and NLRP3 oligomerization [84]. This molecule resulted safe in both mice and humans during preclinical and phase I trials, reducing IL-1β and IL-18 release [84]. A subsequently phase II trial showed the OLT1177 effect on gout flare and in osteoarthritis: in 18–80 years patients with monoarticular monosodium urate crystal-proven gout flare, the oral administration of OLT1177 reduced the joint pain and inflammation, whereas in osteoarthritis, a topical preparation of OLT1177 alleviated severe knee pain [85].

Also hydroxybutyrate, an endogenous ketone body, showed inhibitory action on NLRP3 inflammasome probably by decreasing intracellular potassium. In a cryopyrin-associated periodic syndromes murine model, the oral delivery of exogenous hydroxybutyrate abolished inflammation [86]; in addition, in a gout murine model it blocked NLRP3 priming and activation phases in neutrophils [87]. Furthermore, inzomelid (also known as emlenoflast or MCC7840) is able to bind the NACHT site of NLRP3 and showed a successful outcome in a phase I trial for a patient with cryopyrin associated periodic syndrome [61]. Recently an innovative approach of NLRP3 modulation using an antisense oligonucleotide to target NLRP3 encoding pre-mRNA was used in mice model, resulting in NLRP3 levels reduction with consequent systematic inflammation decrease [88].

Collectively, the reported evidence highlights the importance of pharmacological NLRP3 modulation for regulating inflammatory processes in several disease conditions, and further studies are required to improve both the understanding of their molecular action and to investigate their potential clinical applications. In particular, it will be necessary to understand the clinical relevance of the reported molecules in the landscape of inflammatory diseases therapy through clinical trials, which will be essential to clarify the drug differences in efficacy and safety compared to existing treatments. This kind of studies may also be able to guide the clinical practice, determining how patient and clinical parameters, such as patient age and disease severity, may influence drug effectiveness and toxicity.

6. The Role of NLRP3 Inflammasome in the Drug-Induced Toxicity

Recently emerged evidence indicates that NLRP3 pathway may be involved in the development of drug related side effects and its inhibition may represent a possible strategy to overcome drug-induced toxicity [89]. While the liver and kidney are the organs most frequently involved in adverse drug reactions, the heart, lung, skin, gastrointestinal tract, hematological system, and nervous system may also be affected by drug-induced toxicity [89]. Although the exact molecular mechanisms involving NLRP3 role in the landscape of drug-related toxicity is not completely clear, several studies have been performed confirming the importance of inflammasome in the modulation of drug adverse reactions, leading to hepatotoxicity or nephrotoxicity. This review provides a comprehensive overview of NLRP3's involvement in drug-related side effects, with special emphasis on hepatotoxicity and nephrotoxicity, conditions affecting the primary organs responsible for drug metabolism and excretion.

7. The Impact of NLRP3 Inflammasome in Drug-Mediated Hepatotoxicity

Different studies demonstrated the key role of the NLRP3 inflammasome pathway in acetaminophen-related liver injury. In particular, *in vivo* experiments detected higher expression levels of both NLRP3 and IL-1β in acetaminophen-treated mice liver and hepatic cell lines [90,91] and the knock-out of NLRP3 inflammasome components reduced the hepatotoxicity after acetaminophen treatment [91]. Consistently, the presence of genetic deficiencies in NLRP3 inflammasome components was found to be associated with a lower risk of acetaminophen (paracetamol)-induced liver injury [92]. In addition, studies performed on pediatric patients presenting acetaminophen-related hepatotoxicity or patients with acetaminophen overdose showed increased serum levels of inflammatory cytokines, and monitoring their levels could be considered a promising biomarker to determine the patient's prognosis [93,94]. Similarly, the anticonvulsant drug phenytoin, used for the treatment of epilepsy, may produce drug-induced liver injury characterized by hepatic necrosis [95]. Sasaki *et al.* [96] generated an *in vivo* model to study this type of hepatotoxicity, showing increased NLRP3, HMGB1, and IL-1β liver expression in mice presenting this condition. Evidence also demonstrated a role of NLRP3 inflammasome in the development of hepatotoxicity related to the therapy with triptolide, an immunomodulator derived from traditional Chinese medicine [97]. An *in vivo* study showed that the triptolide-related liver injury was accompanied by higher levels of both serum transaminases and tissue neutrophil infiltration, presenting time-dependent activation of the NLRP3 inflammasome pathway and ROS production [98]. The mice pre-treatment with an inhibitor of caspase-1, Ac-YVAD-CMK, which can block NLRP3 inflammasome activation [99], decreased neutrophil infiltration and the production of pro-inflammatory cytokines, such as IL-1β, TNF-α, IL-6, and Monocyte Chemoattractant Protein-1 (MCP1) [98], underlying the importance of the NLRP3 inflammasome pathway in triptolide-induced hepatotoxicity. Moreover, increased activation of NLRP3 was associated with drug-related hepatotoxicity after therapy with azathioprine [100], carbamazepine [101], and isoniazid [102], confirming the role of NLRP3 inflammasome activation in the development of these adverse reactions and highlighting the importance of monitoring NLRP3 levels, which are crucial for determining the inflammatory status of a tissue and for detecting possible toxicities. Similar situations may occur in the kidney, as described in the next section.

8. The Role of NLRP3 Inflammasome in Drug-Related Nephrotoxicity

A comparable situation was identified for drug-related nephrotoxicity, which is characterized by increased NLRP3 inflammasome levels: augmented NLRP3 expression and consequent increase in pro-inflammatory cytokines were found in both renal tubular and glomerular cells after cisplatin treatment in several *in vivo* models [103,104]. Zhang *et al.* [105] demonstrated an increased amount of purinergic 2X7 receptor (P2X7R), involved in apoptosis and inflammation in the renal tubular epithelial cells of mice presenting cisplatin-induced nephrotoxicity. In contrast, pre-treatment with A-438079, an experimental antagonist of P2X7R, significantly alleviated both cisplatin-induced renal damage and the inflammatory response in the kidney, reducing NLRP3, ASC, caspase-1, and ROS levels [105]. Furthermore, it was found that the caspase-1 inhibitor quinoline-Val-Asp-difluorophenoxymethylketone (QVD-OPH) protected tubular epithelial cells from necrosis after cisplatin treatment and was associated with lower levels of caspase-1, IL-1α, and IL-1β [106]. An *in vivo* study demonstrated that during liver and kidney injury, autophagy also plays a role in the modulation of NLRP3: autophagy reduces NLRP3 availability, thereby affecting its assembly and activation. The cisplatin-mediated inhibition of autophagy may be the basis of the NLRP3 activation in drug-related nephrotoxicity [107]. It was found that nephrotoxicity and cell apoptosis were lower in mice presenting *NLRP3* silencing, which was related to increased autophagy, cellular response to hypoxia, and mitochondrial oxidation [108]. Similar *in vivo* evidence of the NLRP3 involvement in drug-related adverse reactions was detected in a rat model for aminoglycoside gentamicin-induced kidney injury, which was associated with higher NLRP3, caspase-1, IL-1β and TNF-α levels. Interestingly, anti-inflammatory factor C1q/tumor necrosis factor-related protein 6 (CTRP6) reversed the NLRP3 inflammasome activation in a dose-dependent manner in rats presenting gentamicin-induced acute kidney injury [109]. NLRP3 also seems to be involved in nephrotoxicity induced by methotrexate: *in vivo* evidence showed that this adverse reaction was associated with the renal overproduction of ROS and NF-κB upregulation, leading to higher NLRP3 inflammasome activation, caspase-1 activation and release of IL-1β [110]. These data on nephrotoxicity highlighted the key role of NLRP3 inflammasome activation in the landscape of drug-related side effects and identified the possible inflammatory players involved in the consequent inflammatory status.

Taken together, the reported observations on both hepatotoxicity and nephrotoxicity described the possible mechanisms by which NLRP3 is modulated during drug-related adverse reactions, suggesting the importance of monitoring NLRP3 levels to predict these side effects and counteract them rapidly with different strategies, such as treating patients with NLRP3-inhibiting molecules. Also, the ability to predict the onset of drug-related side effects is fundamental to improving the outcome of pharmacological treatments related to the inflammatory status mediated by NLRP3 activity. In this context, NLRP3 methylation level detection consists of a possible biomarker to improve the

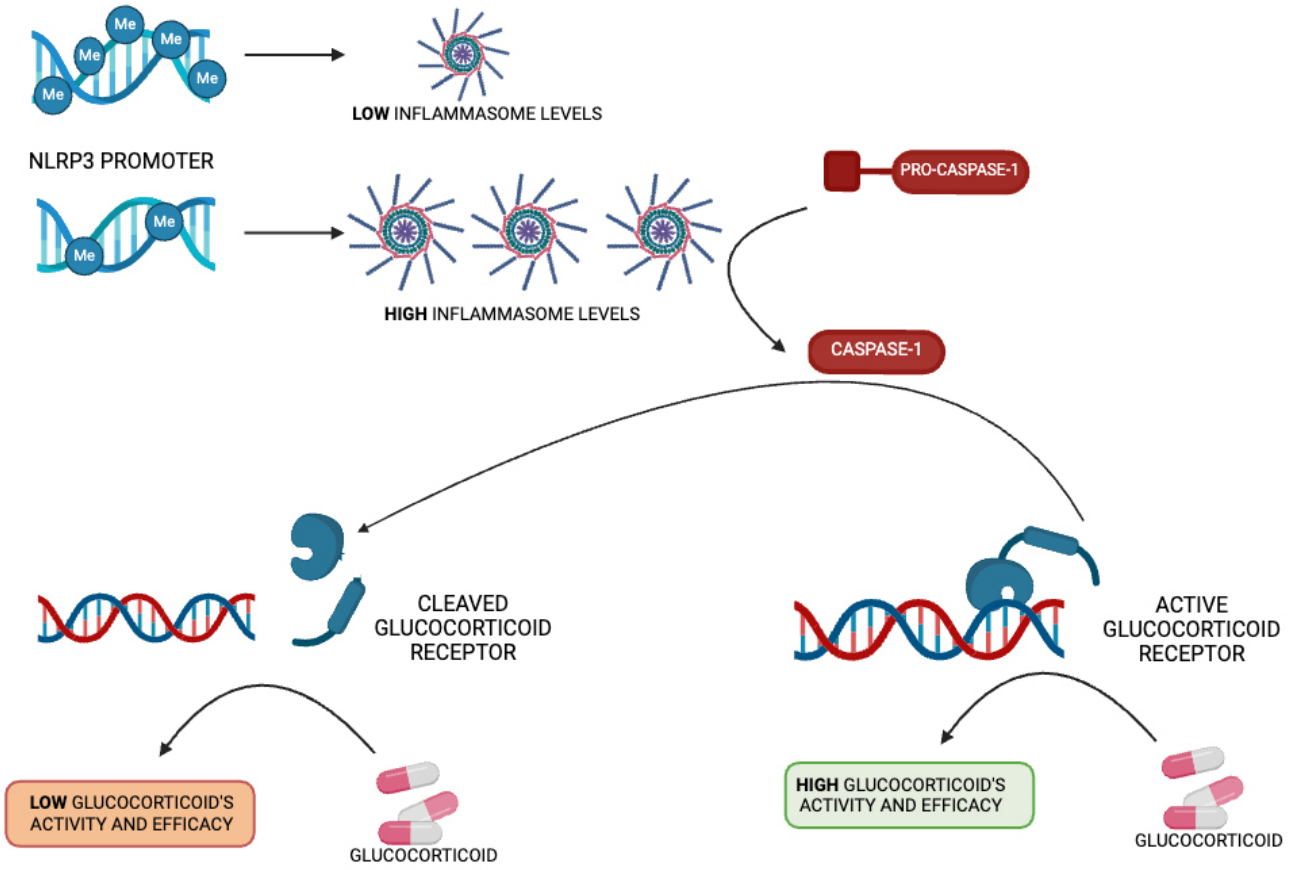

Fig. 2. NLRP3 methylation as a glucocorticoid response biomaker. Schematic representation of the NLRP3 promoter methylation level as a regulator of glucocorticoid response.

anti-inflammatory precision therapy, as deeply described in the next paragraph.

9. NLRP3 Level as a Biomarker for Drug Efficacy and Response

The importance of NLRP3 expression and activity in the inflammatory processes and their modulation has been thoroughly demonstrated. Indeed, the potential role of NLRP3 as a biomarker for clinical disease management has been investigated in various inflammatory syndromes. Currently, different inflammatory markers, such as C-reactive protein (CRP), TNF-α, IL-18, and IL-1β cytokines, can be used as prognostic factors in several diseases [111–113]. NLRP3 levels have become a new possible disease prognostic marker in different pathological conditions. It was recently demonstrated that NLRP3 inflammasome levels were associated with the prognosis of 297 acute coronary syndrome adult elderly patients with differences in sex, smoking status, hypertension, previous medication history and clinical parameters. NLRP3 inflammasome levels were independent predictive factor for other acute coronary syndrome prognostic factors, such as TRS-2P, underlying its efficacy as a disease biomarker [114], whereas another study found that NLRP3 methylation may predispose to depression-related brain structural changes by increasing NLRP3 inflammasome activity [115].

In recent years, different studies have evaluated the possible impact of genetic and epigenetic factors that modulate NLRP3 levels, demonstrating their ability to predict anti-inflammatory therapy response in different disease conditions. In particular, epigenetic factors, such as DNA methylation, change with growth [116] and modulate the expression of different genes involved in drug response [117,118]. Similarly, NLRP3 methylation levels have been investigated to evaluate their potential as biomarkers for glucocorticoid therapy response. Paugh *et al.* [119] identified for the first time the mechanism underlying the epigenetic regulation of the NLRP3 inflammasome in relation to glucocorticoid resistance in pediatric patients with acute lymphoblastic leukemia. In particular, the authors found that the level of promoter methylation of both NLRP3 and caspase-1 regulates glucocorticoid receptor amount, thereby modulating cell sensitivity to steroids (Fig. 2). It was shown that the overexpression of caspase-1 in a human leukemia cell line resulted in the cleavage of the glucocorticoid receptor, diminishing the glucocorticoid-induced transcriptional response and leading to higher drug resistance. The caspase-1 silencing or inhibition significantly

increased glucocorticoid receptor levels, mitigating steroid resistance. They also demonstrated the fundamental role of NLRP3 in drug resistance modulation: the overexpression of CASP-1 alone, without activation via NLRP3, was not sufficient to alter leukemic cells' sensitivity to glucocorticoids [119]. Consistently, Lucafò *et al.* [120] identified a correlation between NLRP3 promoter methylation levels and glucocorticoid-resistance in both adult and pediatric patients with idiopathic nephrotic syndrome. NLRP3 promoter methylation was significantly lower in steroid-resistant patients. Interestingly, on *in vitro* models, NLRP3 knock-down increased glucocorticoid sensitivity, whereas higher NLRP3 inflammasome activation led to a glucocorticoid receptor reduction, which was the basis of higher cellular drug resistance, thereby demonstrating a new molecular mechanism underlying steroid resistance in patients with idiopathic nephrotic syndrome [120]. The ability of NLRP3 methylation to serve as a good biomarker of glucocorticoid response was also reported in IBD patients [121]. Recent results demonstrated that steroid response is significantly associated with lower NLRP3 methylation levels in pediatric IBD patients. Moreover, the patients' disease activity score negatively correlated with NLRP3 methylation before starting the therapy and after 1 month of methylprednisolone treatment. However, no significant association between the patients' disease activity score or steroid response and NLRP3 methylation levels was found in adults IBD patients, whereas in those subjects, a significant positive correlation between age and NLRP3 methylation emerged, indicating that this epigenetic modification of NLRP3 changes throughout the patients' lifespan with different clinical implications for pediatric and adult IBD forms [121].

Several recent studies have demonstrated other possible epigenetic mechanisms underlying the modulation of NLRP3 levels and affecting the drug response. Dai *et al.* [122] found that the lncRNA LINC00969 promotes gefitinib resistance in tumoral *in vitro* and *in vivo* models, affecting the levels of NLRP3 transcriptional m6A modification, which is an RNA post-transcriptional modification important for gene expression regulation, tumorigenesis, and drug resistance [123]. In particular, higher expression of LINC00969 in lung cancer cells with acquired gefitinib resistance could be due to the ability of this lncRNA to modulate the NLRP3 promoter transcriptionally and modify NLRP3 m6A levels. These alterations reduce inflammasome expression and block the NLRP3-mediated pyroptosis signaling pathway, promoting cancer drug resistance [122]. PTEN is a tumor suppressor that affects NLRP3 activation by directly stimulating its assembly or negatively regulating the PI3K/AKT signaling pathway, which regulates NLRP3 phosphorylation [124]. Meanwhile, BRCC3 is a deubiquitinase able to promote inflammasome phosphorylation by removing ubiquitin chains from specific lysine residues on NLRP3 [44]. Interestingly, Cheng and colleagues [125] detected that microRNA-21 blocks the expression of PTEN and BRCC3, inhibiting NLRP3 inflammasome assembly and stimulating cancer cell drug resistance to cisplatin. Furthermore, several studies have identified the epigenetic modulation of NLRP3 levels as crucial for insulin resistance [126,127].

Together, the reported evidence highlights the crucial effect of NLRP3 level regulation, particularly by epigenetic factors, in predicting the pharmacological response to several therapies used for different pathologies presenting similar inflammatory characteristics. Indeed, further studies are required to deeply investigate the epigenetic regulation mechanisms affecting inflammasome levels to confirm the potential role of NLRP3 levels as possible pharmacological biomarkers able to predict drug efficacy.

10. Conclusions

This review thoroughly describes the crucial role of NLRP3 inflammasome in innate immune system activation and inflammation modulation. As reported, NLRP3 tight regulation is sustained by several cellular, genetic and epigenetic mechanisms, and its dysregulation is associated with several cancerous and chronic inflammatory diseases, including IBD, arthritis, gout, Alzheimer's disease and type-2 diabetes. Several pharmacological compounds have been identified as NLRP3 modulators *in vitro* and *in vivo* models, and some of them have undergone clinical trials; however, further studies and trials are required to fully elucidate how these drugs can improve the existing therapies for inflammatory diseases both in terms of efficacy and safety.

A critical need exists for developing reliable pharmacological biomarkers that can predict patient responses to anti-inflammatory drugs. This review synthesizes emerging evidence supporting NLRP3 levels as promising candidates for personalizing therapeutic approaches, particularly for anti-inflammatory treatments that serve as primary interventions across multiple inflammatory pathologies.

Together, the collected evidence indicates that NLRP3 methylation level represent a reliable biomarker of pharmacological steroid response across multiple inflammatory disorders, highlighting its potential translatability across different inflammatory pathologies that require anti-inflammatory treatments.

Author Contributions

GZ, SS, ML, JA and GS wrote and revised the manuscript; GZ, SS, JA and ML designed the manuscript; GS and ML conceptualized the manuscript; GZ, SS, ML, JA and GS revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL39537.

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