

## REVIEW ARTICLE

## Inflammasome, Inflammation, Infection and Mefenamic Acid

Prabhu Kasture<sup>1</sup>, Ketan Mehta<sup>2</sup>, Ambanna Gowda<sup>3</sup>**Abstract**

Nucleotide-binding oligomerization domain like receptors (NLRs) –intracellular proteins, are a recently discovered class of innate immune receptors that play a crucial role in initiating the inflammatory response following pathogen recognition. The dysregulation of NLRP3 inflammasome can cause uncontrolled inflammation and drive the development of a wide variety of human diseases. Mefenamic acid which belongs to fenamate group inhibits the NLRP3 inflammasome by inhibiting efflux of chloride ions and influx of calcium ions through blocking VRAC and TRPM2 respectively. Thus, Mefenamic acid provides a potentially practical pharmacological approach for treating NLRP3- driven diseases.

**Introduction**

Inflammasomes, first identified in 2002, are a class of cytosolic complexes of proteins that mediate the activation of potent inflammatory mediators. They are integral parts of the innate immune response against the invading pathogens and get activated upon infections or stressors that promote release of pro-inflammatory cytokines, triggering a cascade of inflammatory responses.<sup>1</sup>

The nucleotide-binding oligomerization (NOD) like receptors (NLRs), a type of pattern recognition receptors (PRRs) which detect both the endogenous products or exogenous pathogenic microbes<sup>2,3</sup> are important components of inflammasomes and are located within the cytoplasm which recognize pathogen / damage-associated molecular patterns (PAMPs/DAMPs).<sup>4,6</sup>

There are 4 known inflammasomes (NLRP1, NLRP3, NLRP4, and AIM2 inflammasomes) and NLRP3 inflammasome has shown to play an important role in the immune response and therefore has been the most studied amongst all these inflammsomes.<sup>7,8</sup>

NLRP3, a multiprotein complex consists of a scaffold, an adaptor-apoptosis speck-like protein (ASC) and effector procaspase-1, which initiates the formation of the inflammasome by interacting with ASC, which further

recruits and activates procaspase-1 to generate active caspase-1 and then converts the cytokine precursor's pro-IL-1 $\beta$  and pro-IL-18 into mature and biologically active IL-1 $\beta$  and IL-18, respectively. Once activated, these active interleukins trigger a series of inflammatory responses and pyroptotic cell death.<sup>9-11</sup>

**Source and Activation of NLRP3 Inflammasome**

The NLRP3 inflammasome are mainly formed in the bone marrow derived cells-macrophages to the stimulation of pathogenic factors like bacterial toxins, particulate matter, and lipopolysaccharide (LPS).<sup>26,30</sup>

Several molecular and cellular events like ionic mobilization, mitochondrial dysfunction, lysosomal disruption and reactive oxygen species (ROS) production have been proposed for its activation.<sup>5,12</sup> It was shown that the NLRP3 inflammasome can spontaneously assemble if potassium levels get lowered below the physiological intracellular concentration of 70 Mm.<sup>13</sup>

**Ionic Mobilization**

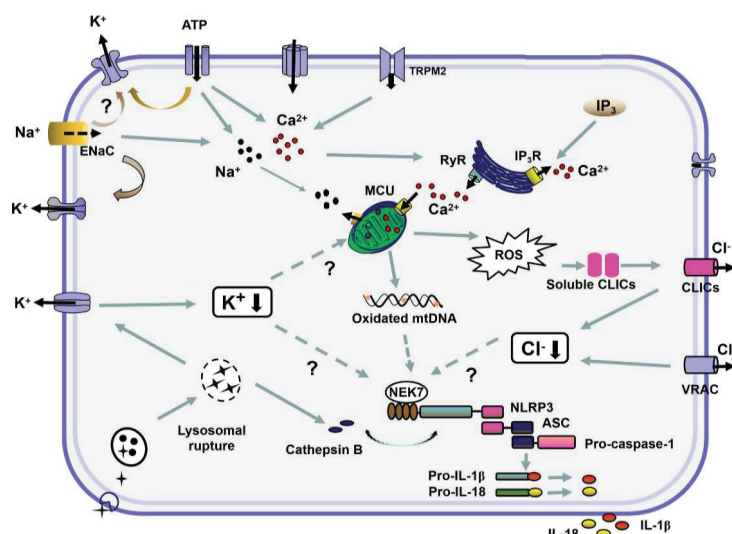
Abnormal influx of Na<sup>+</sup> ions along with efflux of K<sup>+</sup> ions seems to be

responsible for activating the NLRP3 inflammasome, however Na<sup>+</sup> ions alone are insufficient to induce the activation.<sup>12</sup> Cl<sup>-</sup> channels too that have been identified to regulate the NLRP3 activation and include both the volume-regulated anion channel (VRAC) and chloride intracellular channels (CLICs).<sup>14,15</sup> Due to the mitochondrial damage and production of oxidative stress the CLICs get translocated to the plasma membrane and induce efflux of chloride ions (Figure 1).<sup>14,15</sup> Literature has identified NSAIDs belonging to fenamate class like mefenamic acid, flufenamic acid inhibit the membrane Cl<sup>-</sup> channels (VRAC) and are selective inhibitors of the NLRP3 inflammasome.<sup>15</sup> Calcium mobilization from various sources as endoplasmic reticulum (ER), lysosome lumen and extracellular milieu, leads to activation of NLRP3 inflammasome. The extracellular calcium influxes via the plasma membrane cation channel known as transient receptor potential melastatin 2 (TRPM2) (Figure 1)<sup>16,17</sup> and activation of TRPM2 channels increases the NLRP3 activity and IL secretions, intensifying inflammation and cytokine storm.<sup>18</sup> Fenamate analogues like flufenamic acid, mefenamic acid, niflumic acid are found to inhibit the transient receptor potential melastatin 2 (TRPM2) channels and thereby reduce the calcium influx.<sup>19</sup>

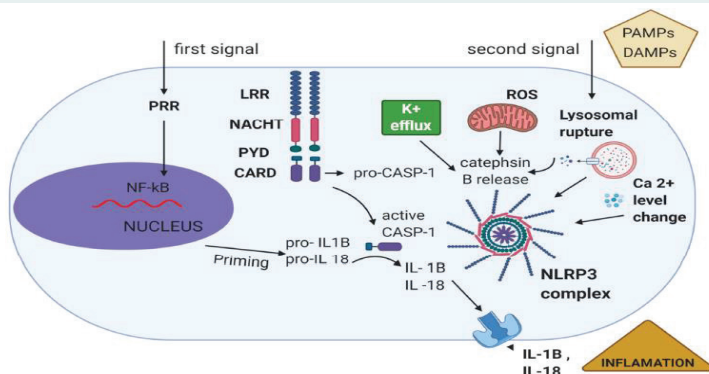
NLRP3 inflammasome activation is a self-defending mechanism against invading pathogens and their components assemble and oligomerize which leads to cleaving of procaspase-1 and forming active caspase-1 which are responsible for transforming the pro-inflammatory cytokines into their mature forms, leading to inflammatory response.

The activation of the NLRP3

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**Fig. 1: Role of ion mobilization in activation of NLRP3 inflammasome**



**Fig. 2: Activation of NLRP3 inflammasome**

inflammasome occurs in two-stages as sensing and assembling. The first stage which begins with the recognition of PAMPs and DAMPs by TLRs which further activates the NF- $\kappa$ B signalling, resulting in elevated production of precursor proteins, including the NLRP3 protein, pro-IL-1 $\beta$ , and pro-IL-18. The second stage is the assembly and effector stage, which begins with the assembly of the NLRP3 inflammasome. The NLRP3 protein, ASC, and procaspase-1 assemble into the mature complex, which then transforms the immature forms of IL-1 $\beta$  and IL-18 into their mature forms, to participate in the inflammatory effect (Figure 2).<sup>1</sup>

The activation of the NLRP3 inflammasome contributes to the host defense against microbial infections. However, when dysregulated, the NLRP3 inflammasome is implicated in the pathogenesis of several inflammatory disorders. Therefore, it is critical that NLRP3 inflammasome activation is precisely regulated to

provide adequate immune protection without causing damage to the host tissues.<sup>20</sup>

### Inflammasome, Inflammation and Associated Diseases

Inflammation represents an immune response of the host to damaging stimulation, realized by pathogens or irritants. Persistent inflammation leads to development of chronic diseases, such as autoinflammatory or autoimmune disorders, neurodegenerative diseases, metabolic conditions, and cancer.<sup>21</sup>

NLRP3 being non selective gets activated with a wide variety of factors leading to secretion of pro-inflammatory cytokines, driving the chronic inflammation.<sup>22</sup>

Aberrant NLRP3 inflammasome activation is linked with the development of many diseases and it has been implicated in the pathogenesis of a number of complex acute and chronic diseases, such as coronary heart disease, pericarditis, stroke, pneumonia, acute kidney injury,

inflammatory bowel disease, ulcerative colitis, type 2 diabetes, atherosclerosis, dysmenorrhea, periodontal disease, obesity, chronic liver disease, non-alcoholic steatohepatitis (NASH), gout, osteoarthritis, neuroinflammation-related disorders (e.g. multiple sclerosis, encephalomyelitis, brain infection, acute injury, neurodegenerative diseases, Alzheimer's disease, Parkinson disease). NLRP3 inflammasome is also linked with various cancers, such as colon cancer, breast cancer, melanoma, hepatitis C virus-associated hepatocellular carcinoma, and gastrointestinal cancers.<sup>4,23,41</sup> Persistent and abnormal NLRP3 signalling is the basis for all these diseases.<sup>24-41,60</sup>

### NLRP3 Inflammasome and Infections

Inflammasomes play a crucial role in innate immunity by serving as signaling platforms which deal with a plethora of pathogenic products (exogenous) and cellular products (endogenous) associated with stress and damage.<sup>24</sup>

Inflammasomes are multi-molecular complexes that contain many copies of receptors that recognize the molecular structures of cell-damaging factors and pathogenic agents as already mentioned earlier. Exposure to viruses, bacteria, yeasts or parasites, can induce uncontrolled inflammation.<sup>42</sup> Multiple scientific reports have demonstrated that viruses entering the body activate an innate immune response in which inflammasomes play a crucial role in pathogen destruction.<sup>43-45</sup>

There are two systems of first-line of defense against viruses: the production of Type I interferons and the production of the cytokines IL-1 $\beta$  and IL-18 by inflammasomes. Type I interferons promote an antiviral state in the infected host, whereas cytokines have antiviral effects by inducing inflammatory processes and modulating adaptive immune responses.<sup>46</sup>

Several studies have demonstrated that infection of cells with the various pathogenic micro-organisms (viruses, bacteria, fungi and protozoa) like influenza A virus (IAV), Human immunodeficiency virus (HIV), Enteroviruses, Epstein Barr virus (EBV), corona viruses, dengue viruses, Zika virus, Helicobacter Pylori, Mycobacterium Tuberculosis, Salmonella Typhimurium, Brucellosis,

*Streptococcus pneumoniae*, *Malassezia*, *Microsporium canis*, *albicans*, *Aspergillus*, *Paracoccidioides brasiliensis*, *Neospora caninum*, *Leishmania*, *Entamoeba histolytica*, *Schistosoma* induces the assembly of inflammasome complexes and IL-1 $\beta$  and IL-18 secretion.<sup>47-51</sup>

During host defense against microbial infections, a prominent role is played by the pattern recognition receptors (PRRs) which include membrane bound Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) and non-membrane bound AIM2-like receptor (ALR), RIG-I-like receptor (RLR), nucleotide-binding protein domain and leucine-rich repeat-containing (NLR) proteins. Activation of these receptors upregulates the inflammasome activity that helps in controlling these microbial pathogens. Further an imbalance in the ionic concentrations in the cells (Na, K, Ca, Cl), generated by damaged mitochondria ROS or lysosomal rupture due to microorganisms, lead to activation of NLRP3 inflammasome and release of IL-1 $\beta$ .<sup>52</sup> Thus, it can be understood that Inflammasomes are activated by a wide range of stimuli such as: pathogenic toxins and components (eg. Lipopolysaccharide (LPS), bacterial flagellin, SARS-CoV E, viroporin proteins, etc.) and endogenous components (eg. DAMPs, PAMPs, K<sup>+</sup> efflux, cathepsin B release, amyloid- $\beta$ , etc.).<sup>42</sup>

It is evident from the literature data that the host activates the mechanism of inflammasomes formation as a defense response against the described pathogenic microorganisms, but in turn, some pathogens using their virulence factors may antagonize inflammasome pathways and increase their ability to survive in the host and cause disease. The host organism then expresses excessive amounts of inflammasomes to remove harmful factors, which leads to the overproduction of inflammatory cytokines and can cause excessive inflammation.

#### **Mefenamic acid and NLRP3 Inflammasome**

Mefenamic acid belonging to the class of NSAIDs and fenamate family, is a versatile agent with an established antipyretic, analgesic and anti-inflammatory actions. These actions of Mefenamic acid are related to its preferential COX inhibition and EP receptors blockage both centrally

and peripherally.<sup>53</sup>

Given the role of NLRP3 inflammasome in many of acute and chronic diseases, there is a great potential in developing NLRP3 inflammasome inhibitors as therapeutic options. Cytokines like interleukins-1 $\beta$  play a key role in causing inflammation; hence, blocking their effects through NLRP3 inhibition can be effective in the treatment of several conditions like rheumatoid arthritis, psoriasis, dysmenorrhea, inflammatory bowel disease and other auto inflammatory diseases as discussed in this review.<sup>1</sup> Following an infection or injury, the components of inflammasome collect, oligomerize, and assemble to cleave procaspase-1 to its active form. This activation facilitates the conversion of pro-inflammatory cytokines to their active forms (pro-interleukin (IL)-1 $\beta$  and pro-IL-18 to active form IL-1 $\beta$  and IL-18), causing an inflammatory response. It is well understood that the inhibition of aberrantly activated NLRP3 inflammasome can be an important therapeutic target in the array of inflammatory diseases as discussed herein.<sup>53</sup>

NSAIDs of the fenamate type such as flufenamic acid and mefenamic acid have shown to inhibit NLRP3 inflammasome by reversibly blocking volume-regulated anion channels, which regulate Cl<sup>-</sup> transport across plasma membrane and also the volume-modulated transient receptor potential (TRP) channels.<sup>15,19</sup>

NSAIDs also contribute to limiting the secretion of proinflammatory cytokines through their conventional action on the cyclooxygenase enzyme.<sup>54</sup>

Evidences from in vitro and preclinical studies have demonstrated, mefenamic acid and flufenamic acid to have the potential neurotoxic inflammatory reducing response through their potent NLRP3 inflammasome inhibition.<sup>55,56</sup>

Increased NLRP3 can mediate IL-1 $\beta$  secretion that is responsible for the occurrence of febrile seizures (FS) and FIRES, thus the NLRP3 inflammasome inhibitory action of mefenamic acid may attenuate the pro-inflammatory cytokine (IL-1 $\beta$ ) levels.<sup>53</sup>

Accumulating evidence derived from investigations and clinical observations converges to implicate the auto inflammatory nature of febrile illness related epilepsy syndrome

(FIRES). A closer analysis suggests excessive activation of microglial / NLRP3 inflammasome / IL-1 axis might represent the pivotal event in FIRES, which creates a pro-inflammatory and pro-convulsive milieu.<sup>57</sup>

In the first-ever study in humans, it has also been shown that mefenamic acid may be used as a neuroprotector. Mefenamic acid in dosage of 500 mg twice daily was safely administered for six months. The anti-inflammatory activity of mefenamic acid, particularly targeting the NLRP3 inflammasome pathway, improved cognitive impairment and reversed memory loss and brain inflammation.<sup>58</sup>

It is evident from the literature that aberrant activation of NLRP3 inflammasome plays a key role in the pathogenesis of SARS-CoVs diseases progressing to hyper immune response and cytokine storm. The promising results obtained after repurposing of mefenamic acid in covid-19 patients may be related to its synergistic anti-inflammatory action on the COX enzymes and NLRP3 inflammasome, which potentially might have decreased the excessive inflammation, relieved the pain and fever associated with this viral infection.<sup>59</sup>

#### **Conclusion**

Inflammasomes play a crucial role in innate immunity by serving as signalling platforms which deal with a plethora of pathogenic products and cellular products associated with stress and damage.

Aberrant activation of the NLRP3 inflammasome and release of excess interleukin IL-1 $\beta$  is implicated in various acute and chronic inflammatory diseases. Aberrant activation of inflammasome / IL-1 $\beta$  axis in febrile seizures and FIRES is also evident from clinical observations. Thus, inhibition of NLRP3 will help alleviate the excess inflammation associated with these various conditions.

Only fenamates like mefenamic acid and flufenamic acid have shown to inhibit the NLRP3 inflammasome, which may help reduce the excess secretion of pro-inflammatory cytokine IL-1 $\beta$ . Anti-inflammatory action of Mefenamic acid may thus get augmented with the NLRP3 inhibitory action, which has been evident from the literatures and recent clinical evidences. The usual therapeutic dose



recommended for Mefenamic acid is 500 mg thrice daily for adults and 25 mg/kg /day in three divided dosages for children above 6 months of age. Thus, with this understanding and corroborating evidences, Mefenamic acid seems promising in situations of dysregulated NLRP3 inflammasome conditions and should be explored clinically as relevant.

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