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Research Paper

Involvement of NLRP3 Inflammasome in Rhinosinusitis

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Abstract
Inflammasome is a multiple protein complexes of cytosol, which traditionally comprised of the NOD-like receptor (NLR) family of upstream sensor proteins, ASC adaptor protein, and the caspase-1 downstream effector. Inflammasomes recognition protein is the receptor protein which contributes to caspase-1 auto cleavage and stimulation. Modified caspase-1 causes the processing and activation of interleukin-1β and interleukin-18 pro-inflammatory cytokines. Rhinosinusitis is characterized by inflammation in nose and paranasal sinuses leads to interruption or conversely nasal discharge or a runny nose that may flush from front or back of nose. Chronic sinusitis can be caused by an infection or growth and it can be last up to eight weeks. NLRP3 Inflammasome is involved indirectly in the progression of rhinosinusitis by stimulating the production of interleukins (IL-1β and IL-18). Interleukins promote the inflammatory growth in nasal and paranasal sinuses.

Keywords: *NLRP3 Inflammasome, Rhinosinusitis, Nasal polyps, IL-1β, IL-18 and procaspase-*

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I. Introduction

As increasing consequences of inflammatory diseases in the society, their mechanistic pathway remains to be explored in the researcher's society. NLRP3 Inflammasome got attention and is getting explored nowadays because of its involvement in various diseases and signaling pathways. NLRP3 is a dimeric protein which gets assemble when it gets activated by its NLRP3 gene[1]. NLRP3 is an 115KD a cytosolic protein abundant in monocytes, Neutrophils, Dendritic cells, Lymphocytes, Osteoblast and epithelial cells. NLRP3 may be triggered by a wide range of stimuli following this priming stage, which include ATP, K+ ionophores, Heme, Particular matter, Pathogens related RNA, bacteria, fungal toxins and its components. NLRP3 Inflammasome activation is finely managed to offer appropriate immune protection without causing injury to the host tissue[2]. Normally, pathogens and dendrites stimulate the inflammatory cascade by acting on toll like receptors and interleukins receptors. Hence, once the receptors will get activated it promotes the signaling pathway of NF-κB and finally leads to the activation of NLRP3 genes. NLRP3 Inflammasomes are responsible for the production of the procaspase-1 which converts the proinflammatory interleukins. However, NLRP3 plays significant role in disease of the central nervous system such as- Alzheimer's and Parkinsonism disease[3]. Abnormal activation of NLRP3 Inflammasome is responsible for Intestinal cancer, inflammatory disease (Crystal Arthropathies, Periodic fever syndrome & Rheumatoid Arthritis) and Auto- inflammatory disease such as- Keratitis or Conjunctivitis. Rhinosinusitis is the condition of inflammatory sinuses in mouth and nose; hence interleukins and other inflammatory mediators are involved in its pathogenesis. Sometimes these interleukins are produced by NLRP3 Inflammasomes and are responsible for the rhinosinusitis condition[4]. An inflammasome denoted by its sensory proteins (a PRR), which are oligomerized to create a pro-caspase-1 activating then response to DAMPs or PAMPs. Mainly five PRRs sensor protein have been established to caused inflammasomes. Nucleotide binding oligomerization domain (NOD), Leucine rich repeat (LRR) comprising protein such as- NLRP1, NLRP3, NLRC4 while also absent in melanoma-2 (AIM-2) and pyrin. And some other member of PRRs also involved in inflammasome like- NLRP2, NLRP6, NLRP7, NLRP12 and IFI16[5].

II. Rhinosinusitis

Rhinosinusitis, previously referred as sinusitis, is an inflammatory condition which affects nose and paranasal sinuses. Symptoms such as facial pain/pressure, nasal congestion or rhinorrhea, hyposmia or anosmia are the basis of defining rhinosinusitis[6]. Acute rhinosinusitis and chronic rhinosinusitis are the two types of rhinosinusitis predicated on the duration of symptoms. In Acute Rhinosinusitis, there is a sudden emergence of two or more symptoms which lasts less than 12 weeks, while these symptoms continue for more than 12 weeks in chronic rhinosinusitis. The two phenotypes of chronic rhinosinusitis which have been differentiated are chronic rhinosinusitis with nasal polyps (CRWNP) and chronic rhinosinusitis without nasal polyps (CRWONP)[7]. To evaluate whether the NLRP3 Inflammasome and IL-1β are expressed in different polyp tissue subsets, we determined the presence of eosinophils, neutrophils, NLRP3, and IL-1β in nasal tissues by hematoxylin and eosin for eosinophils and immunohistochemically staining for neutrophils, NLRP3, and IL-1β. There are four divisions of the polyp tissues are: Eosinophilic and Neutrophilic (EOS^+ NEU^+), Non-eosinophilic and Neutrophilic (EOS^- NEU^+), Eosinophilic and Non-neutrophilic (EOS^+ NEU^-) and Non-eosinophilic and Non-neutrophilic (EOS^- NEU^-)[8]. The most prevalent and complicated one between acute rhinosinusitis and chronic rhinosinusitis is chronic rhinosinusitis. The main mechanism which is involved in the pathogenesis is inflammation and tissue remodeling. The Sino nasal epithelium serves as a defensive shield against external factors, with the mucus blanket providing additional protection. The dysfunction of epithelial barrier due to certain factors such as defects in tight junction proteins, transport system, decrement of protective enzymes may result in reduced epithelial resistance, augmented absorbance of bacterial endotoxins, acanthosis and acantholysis [9]. All of these are significantly involved in the pathogenesis of the disease. Apart from impaired Sino nasal epithelium, the dysregulated host immune system also contributes in CRWNP and CRWONP[10]. Levels of cytokines and cells such as eosinophils, basophils, mast cells are elevated during chronic rhinosinusitis due to the activation of innate and adaptive immune responses. These cells release inflammatory mediators that can maintain the inflammatory response of chronic type-2 and inflict damage to the Sino nasal mucosa[11]. Low-Dose and long- term administration of Macrolide antibiotics is basic treatment of chronic rhinosinusitis in Japan; So, Macrolide therapy was discovered in japan as a treatment for Diffuse Pan bronchiolitis (DPB) [12].

2.1. Mechanistic pathway of Rhinosinusitis

Mechanism behind the development of rhinosinusitis is still poorly understandable and there may be an overlap of infective, Allergic and host response mechanism that lead to development of symptoms. Viral and Bacterial infection cause production of inflammatory mediator Bradykinin, which caused pain related symptoms such as- Sore throat pain, Sinus pain, Irritation of sensory nerve can trigger sneezing and runny nose as well as nasal congestion[13]. Whereas, the allergic reaction caused due to the release of the histamine from mast cell in the airway epithelium leads to inflammation. The symptoms of Rhinosinusitis can be classified as- Systemic symptoms (Fever, Headache, Fatigue, Mood change, Muscles aches and pain) or Local symptoms (Itching, sneezing and nasal decongested) Nasal discharge found in both Acute and Chronic rhinosinusitis [14]. The nasal discharge attributed with rhinosinusitis is a complex mix of elements obtained from glands, goblet cells, plasma cells, and plasma exudate from blood vessels, and the relative significance from these various sources varies with time and severity of the inflammatory response. The colour of nasal discharge and sputum is frequently used as a clinical marker to determine whether or not to prescribe antibiotics. During the course of a viral infection, the colour of nasal discharge may change from clear to yellow to green, and this colour change is associated to a recruitment of leukocytes into the airway lumen and is a hallmark of airway disease[15, 16]. Cough is common symptom associated with acute viral rhinosinusitis, but its association with chronic rhinosinusitis is controversial. Cough is mediated exclusively by the vagus nerve and this means that cough is initiated in the airway by stimulation of sensory nerve at the level of the larynx or below, Cough associated with rhinosinusitis must involve structures at the larynx or below to stimulate vagal nerves. Chronic rhinosinusitis is often associated with allergy and asthma and it is difficult to separate lower airway inflammation from upper airway inflammation in the generation of cough associated with rhinosinusitis[17] (see fig.1).

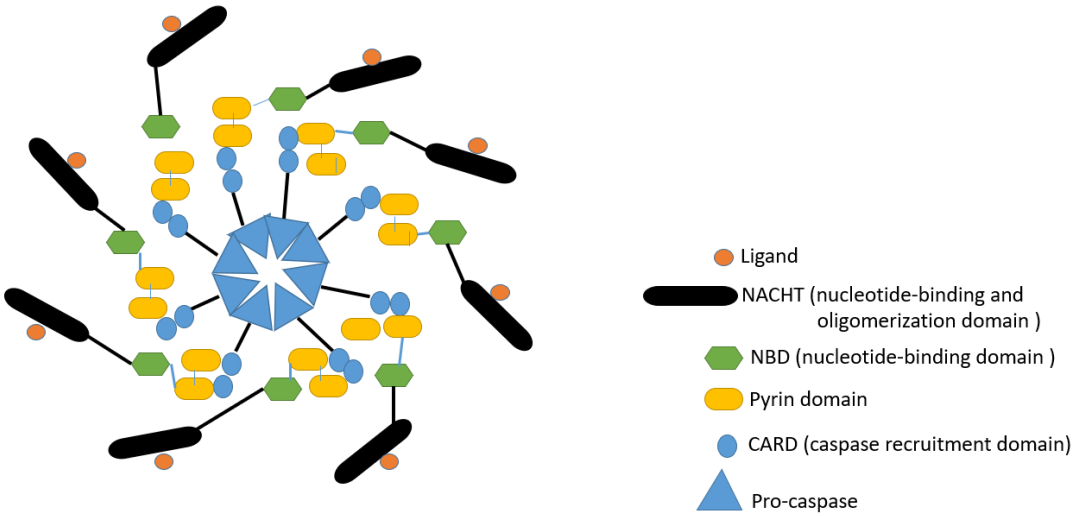

Fig.1 Structure of NLRP3 Inflammasome

III. NLRP3 Inflammasome

NLRs (NOD-like receptors) can associated with a protein to form a complex called- Inflammasome The aggregates are primarily formed by NLRP3 stimuli (such as Nigericin, asbestos, Silica, Alum, and Amyloid beta). These materials are Phagocytosed and afterwards damage the lysosome, causing Cathepsin-B to be released and directly activate NLRP3[18]. NOD Like Receptor Protein 3 (NLRP3) Inflammasomes are the massive structures of protein organized in the cytoplasm in response of hazards such as injury of tissues or infection. When triggered, they stimulate the production of inflammatory cytokine and encourage cells into pyroptosis called as pro-inflammatory death[19]. Initiation of NLRP3 Inflammasome in macrophages involves two steps: priming and activation. The priming step (signal 1) is given by inflammatory stimuli such as TLR4 agonists which induce NF-κB influenced NLRP3 and pro-IL-1β expression, and the activation step (signal 2) is provoked by PAMPs and DAMPs, thereby promoting NLRP3 Inflammasome assembly and caspase-1-mediated IL-1β and IL-18 secretion and pyroptosis. However, the priming stage is sufficient for human monocytes to trigger caspase-1 stimulation and IL-1β release. It should be emphasized that the priming stage is presumably not confined to the NF-κB dependent transcriptional overexpression of NLRP3 and pro IL-1β, since NLRP3 Inflammasome can be triggered as early as 10 min if treated with signal 1 and signal 2 stimuli simultaneously[20, 21].In reference to pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs); an Inflammasome is characterized by its sensor protein (pattern recognition receptors) that oligomerizes to assemble a procaspase-1 activating system. The NLRP3 Inflammasome is important towards microbial, fungal and viral infections for host's immune system.

3.1. Structure of NLRP3 Inflammasome

The N-terminal pyrin domain (PYD), the core domain NACHT, and the C-terminal domain leucine rich repeats make up the NLRP3 protein. NACHT domain proteins include the NLP member apoptosis inhibitor protein, the MHC class II transcription activator, the incompatibility locus protein, and the telomerase associated protein. The Pyrin domain of NLRP3 contains six helices of proteins with five connecting loops which were previously analyzed by X-ray crystallography and solid states NMR[22]. These helices form a canonical anti-parallel helical bundle tuck together by central hydrophobic core of α1, α2, α3, α4, α5 and α6. Pyrin domain and caspase activation & recruitment domain (CARD) are collectively referred as Apoptosis associated speck like protein containing a CARD. Interaction of caspase (CASP) with CARD will leads to the production of pro-caspase 1 from NLRP3 Inflammasome dimer [23].

IV. Involvement of NLRP3 Inflammasome in Rhinosinusitis

Rhinosinusitis is the inflammatory condition of the nasal cavities and paranasal sinuses characterized by the obstruction or nasal congestion or a persistent cough that can flow from front or rear of the nose. Inflammatory cells are produced in response to various pathogenic allergens or other immunogens which leads to the acute or sometimes chronic condition of rhinosinusitis[24]. In CRSwNP groups, there is indeed a substantial link among NLRP3 mRNA levels & caspase-1 mRNA levels, showing that NLRP-3 and caspase-1 work together in the pathogenesis of CRSwNP. In CRSwNP, NLRP3 had a key role in boosting epithelial cell

proliferation as well as inflammatory cell infiltration, and also the impact of NLRP3 is much more pronounced in ECRSwNP. Due to the strong representativeness of HNECs in human nostril polyps and the ease with which HNECs may be isolated from humans nostril polyps, which are frequently used to investigate the control of specific genes in the physiopathology of CRSwNP[25].

NLRP3 stimulates the production of caspase-1 which leads to the further conversion of proinflammatory mediators (pro IL-1β and pro IL-18) and results in the formation of interleukins (IL-1β and IL-18). These interleukins (IL-1β and IL-18) promotes the inflammatory pathways which are responsible for the Inflammation of sinuses[26]. IL-1β induces the expression of genes that control fever, Pain threshold, Vasodilation & Hypotension, IL-18 is responsible for Interferon-Gamma (IFN-γ) production and it is Co-stimulatory cytokine that mediate Adaptive immunity[27]**.** However, NLRP3 Inflammasome was regulated by its NLRP3 Inflammasome gene which was activated through the response of DAMPs and PAMPs. Furthermore, these DAMPs and PAMPs will binds to the toll like receptors (TLR) and stimulate the signaling pathway for dimerization of NLRP3 Inflammasome. However, tumor necrosis factor receptor (TNFR) and interleukins receptors (ILRs) are also get involved in the mechanistic pathway of NLRP3 Inflammasome. Release of interleukins (IL-1β and IL-18) by the activation of procaspase-1 is responsible for the worsening condition of rhinosinusitis due to hypersensitivity and allergic inflammation in mouth and nose[28] (see fig.2).

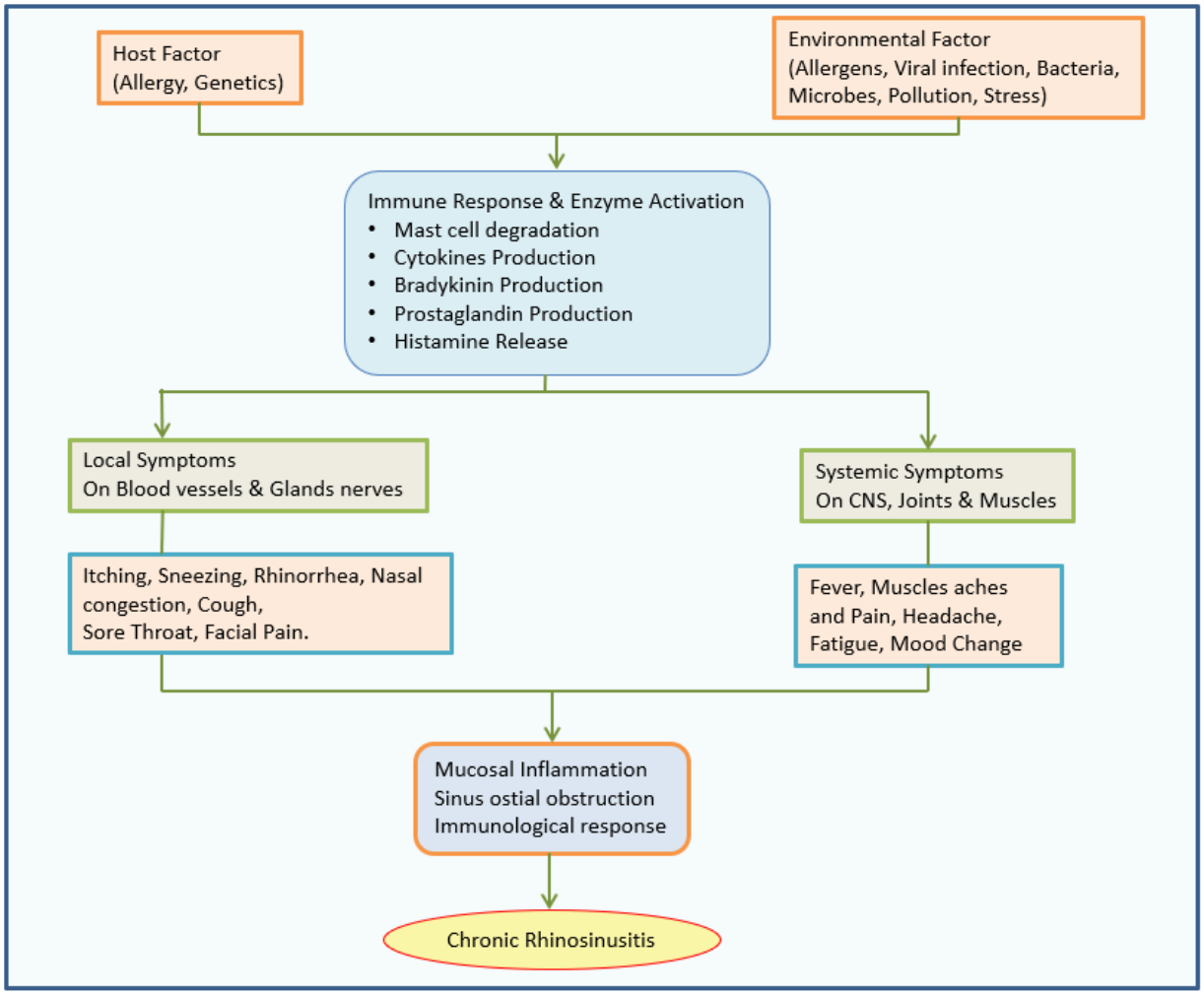

Fig.2 Brief implication of chronic rhinosinusitis occurred due to Host and Environmental factor which involve the immune response activation.

Activation of NLRP3 inflammasome which can lead to Rhinosinusitis

NLRP3, caspases-1, IL-1β and IL-18 play a major role in the disease progression. There was a significant increase in mRNA levels of NLRP3 and caspases-1 in rhinosinusitis[25].

NLRP3 inflammasome is activated by several factors like microbial attack, substances like uric acid, silica fibers, extra cellular ATP, pore forming toxins and α-hemolysin produced by S.aureus etc. this activated NLRP3 is indeed activate procaspase -1 into its active form caspase-1. This activated caspase-1 will interact with the IL-1β, IL-18 and IL-1 and convert them into mature form. This mature factors will trigger the

inflammatory condition known as rhinosinusitis. Some purinergic receptors like P2X7 can also trigger the activation of NLRP3 inflammasome by increasing ATP concentration in cytosolic membrane[29].
There are several mechanisms which explain the activation of NLRP3 inflammasome.

1. Activation by ion channel

P2X7 ion channel is activated by ATP. This activated channel will leak out the potassium ions resulting in cell membrane perforations. Through this perforations the agonists enter into the cytosol and activate the NLRP3 inflammasome.

2. Activation by lysosomes

Lysosomes are get activated by its agonists and release cathepsin molecules. This cathepsins will combine with the NLRP3 inflammasome and activate it. This will lead to activation of caspases and ultimately lead to rhinosinusitis.

3. Activation by Reactive oxygen species (ROS)

In this mechanism the ROS generated by several pathways will trigger the activation of NLRP3 inflammasome[29].

4. Activation through post translational modifications

NLRP3 inflammasome activation is controlled mainly by phosphorylation at serine and tyrosine amino acid residues. Many studies have reveled that NLRP3 dephosphorylation by PTPN22 at Tyr 861 leads to inflammasome activation. In the same way dephosphorylation at ser 5 by PP2A and JNK1- mediated phosphorylation at ser 194 have led to activation of NLRP3 inflammasome. NLRP3 activation is also regulated through ubiquitination. Removal of lysine-48 (K48) and lysine-63 (K63) ubiquitin chains on NLRP3 by BCCR3 leads to NLRP3 inflammasome activationwhich ultimately leads to pathological condition called rhinosinusitis[30].

NLRP3 activation sites

- c- terminal of LRR domine
- NACHT domine
- ADP -bound NLRP3

ATPase activating site within the NACHT domine [1].
NLRP3 inhibitors acts on this particular sites and this is useful in treating rhinosinusitis.

V. NLRP3 Inflammasome inhibiting agents

Listed below are NLRP3 inflammasome inhibitors which are used in treatment of several diseases like myocardial infraction, diabetes, chronic inflammatory diseases and Alzheimer's disease etc. but till now there is only 3 agentsare used for treatment of rhinosinusitis. Clinical trials are going on other agents which are listed below, may be in future they can be used in treatment of rhinosinusitis[29, 31-37].

Agents used in treatment of rhinosinusitis

MCC950: It is a diaryl-sulfonylurea containing molecules, which is regarded as a highly effective and specific NLRP3 inflammasome inhibitors[38, 39]. It indeed attached specifically to a walker-B motif of the NLRP3 NACHT domain that prevent adenosine tri phosphate hydrolysis as well as the development of the whole NLRP3 inflammasome[35]is achieved by inhibiting the formation of NLRP3 inflammasome such as NLRP3-ASC as well as NLRP3 caspase-1 complex, and production of pro-inflammatory mediator like- TNF-α, Interleukins-1β and interleukin-18. MCC950 inhibited spinal neuron damage and NLRP3 inflammasome stimulation by oxygen glucose deprivation or lipopolysaccharide [31, 32]. It also reduces the expression of NLRP3 protein by regulating the translational and post translational modifications[40].It donot inhibit the inflammasome at priming step rather than it inhibits the assembly of NLRP3 inflammasome[41]it is mainly used in the treatment of Alzheimer's diseases and neuroinflammatory diseases[37].An alternative mechanism for the induction of Acute Rhinosinusitis symptoms in the OVA-induced allergic rhinitis paradigm is the NLRP3 inflammasome signaling pathway.OVA -induced mouse model in evaluation of rhinosinusitis, in this the mouse are given MCC950 200µg and 400 µg per kg body weight and control group is given dextran, evaluation is done based on the behavior of mouse after 29 days of treatment. The frequency of sneezing and nose rubbing of mouse after 29 days of treatment is taken. Blood and nasal discharges are collected to evaluate the inflammatory mediator levels in both control and treated group. There is a gradual increase in sneezing,nose rubbing and inflammatory mediators in control group when compared to treated.This results shows thatthe NLRP3 cascade is specifically inhibited by MCC950, which reduces Acute Rhinosinusitis symptoms[42].

A740003 : It iscompetitive antagonist of P2X7R . It may be used as a therapeutic agent for treating rhinosinusitis. It inhibits the activation of NLRP3 by inhibiting P2X7R and decreasing ATP concentration in cytosolic membrane. It is used in the treatment of rhinosinusitis. A study is conducted on patients with chronic rhinosinusitis in that study they used A740003 as a material. In their study they have conformed that with the use of this drug there is a significant decrease in expression levels of P2X7 and as well as NLRP3

inflammasome in treated group when compared to control group. In normal individual the ATP levels are less in extra cellular fluid when compared to diseased individual. This extracellular ATP is used as a triggering molecule for inducing the inflammatory response by activating the P2X7 ATP mediated channel. A740003 act as an antagonist to the P2X7 membrane receptor which triggers NLRP3 inflammasome activation. There by reduce the chances of rhinosinusitis[29].

Deubiquitinases:these agents are used to prevent the ubiquitination of NLRP3 inflammasome there by preventing the activation of NLRP3. Examples for these agents are A20, cezanne, CYLD WP1130, LDN57444, NSC, 1,10-Phenanthroline [30]. In normal individuals these deubiquitinases are expressed but in rhinosinusitis its expression is altered by the bacterial attack or cytokinin release and lead to rhinosinusitis. This is proved by the studies conducted by Ping Li et al. [43]

Some agents which are listed below are involved in inhibition of NLRP3 inflammasome but studies are going on them to know whether they are useful in treatment of rhinosinusitis.

CY-09: It act directly inhibit NLRP3 by suppressing NLRP3 ATPase action & prevents NLRP3 inflammasome initiation by targeting NLRP3. It is a synthetic analogue of CFTR-172, a CFTR transmembrane conductance regulator channel inhibitor. It has a direct interaction with NLRP3 walker A region of NLRP3 that prevents NLRP3 from attaching to adenosine tri-phosphate[35]By blocking the stimulation of inflammasome, the CY-09 lowered the generation of inflammatory cytokines, intracellular Ca2+ concentration as well as TRPA1 stimulation, lowering the pro-inflammatory polarization of macrophages and relieving animals ache and damaged [33, 44]. It is used as a therapeutic agent for treating rhinosinusitis[35].CY-09 could enhance olfactory function in Acute Rhinosinusitis mice, which may be related to preventing the NLRP3-mediated pyroptosis, which is closely related to the Olfactory Disorder connected to Acute Rhinosinusitis[45].

Tranilast: It is chemically N-[3,4-dimethoxycinnamoyl]-anthranilic acid (TR)[37]This drug binds with a NACHT region of NLRP3 to disrupt NLRP3-NLRP3 & NLRP3-ASC interactions TR is indeed a tryptophan metabolite analogue that has been shown to impede homologues selective subcutaneous anaphylaxis [46]. It inhibits NLRP3 inflammasome independently without inhibiting NLRC-4 or AIM-2 inflammasomes[37]. Tranilast inhibit the intrinsic NLRP3-ASC interaction but not the NLRP3-NEK-7 interaction, rising the possibility that it directly target NLRP3[47]. It acts directly by binding to NLRP3 protein and thereby inhibiting oligomerization of NLRP3 inflammasome [49].It is mainly used in treatment of rhinosinusitis[48].

OLT1177 (Dapansutrile): It is a β-sulfonyl nitrile which specifically inhibits NLRP3 inflammasome[37].It specifically inhibits the NLRP3 ATPase which hindered the activation of inflammasome's ASC as well as caspase-1 interaction, which are inhibit the inflammasome from assembling and inflammatory mediator like-Interleukin-1 as well as interleukin-18 from being released. Pyroptosis is also inhibited by the substances[49, 50]. It is the first compound which is proved to be safe for human use[39]. It is mainly useful in treatment of cardiomyopathy and Alzheimer's disease[36, 37].

Glyburide [glibencamide] : It is chemically sulfonylurea medication that is commonly used in Type-2 Diabetes. In pancreatic islet block ATP sensitive K+ channel, it suppresses PAMP, DAMP as well as crystal induced NLRP3 inflammasome initiation in bone marrow derived macrophages. It is specific for NLRP3 but high dose is required to produce therapeutic effect[37].Its suppressive ability appears to be limited to the NLRP3 inflammasome as it had no effect on the production of IL-1 from the activated NLRC-4 or NLRP-1 pathways [34, 51].It is mainly useful in treatment of diabetes as well as in Alzheimer's disease[36, 37].

JC124: -JC124 is a novel NLRP3 inflammasome inhibitorwhich is synthesized by methylating the JC121 a structural analogue of glyburide[36]. In both in vitro and in vivo pathways, JC124 significantly inhibited the NLRP3 inflammasome. The JC124 target also on NLRP3 inflammasome has been identified, and effects on ROS and TNF levels have been demonstrated. As a result, it helps in regulating NLRP3 priming response [52, 53]it is used to treat diabetes as well as Alzheimer's disease and neuro inflammatory diseases[35, 36](see fig.3).

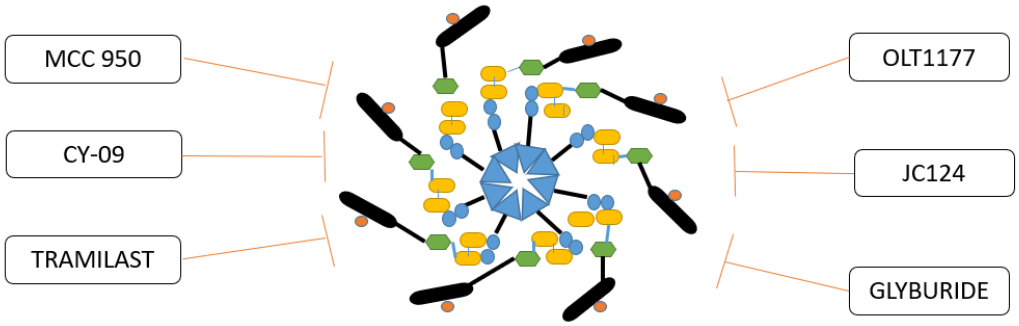

Fig. 3 **Inhibitors of NLRP3 inflammasome**: It is inhibits the formation of NLRP3 Inflammasomes like-NLRP3-ASC, Caspase-1 complex, TNF-α, interleukins-1β and interleukins-18.

Micro RNAs: micro RNA133b is used to decrease the expression of NLRP3, ASC and caspase-1 there by reducing the pathological condition by attenuating the release of eosinophils and mast cells infiltration in the nasal mucosa. it is mainly useful in treating allergic diseases like asthma[54].some micro RNAs like MiR138-5p will act directly on NLRP3 by targeting 3'-UTRthus inhibits the activation of NLRP3 inflammasome. Additionally, MicroRNA-223 targets NLRP3 directly and suppresses its expression, lowering the inflammation caused by LPS in the microglia and enhancing neuronal function. However, some research has discovered that indirectly, microRNAs also influence NLRP3 expression. MiR-194-5p can target TNF receptor associated factor 6 (TRAF6), which collaborates with NLRP3 to encourage NLRP3 inflammasome activation .these agents are used in the treatment of Alzheimer's disease[36].

MNS [3,4-methylene dioxy-β-nitrostyrene]: it is a synthetic nitroalkene which act specific towards NLRP3 inflammasome[35].it prevents oligomerization and activation of NLRP3 inflammasome by inhibiting the ATPase activity and LPS- induction[55]it is mainly useful in treatment of chronic inflammatory diseases and Alzheimer's disease[36].

Oridonin:it is an electrophilic ent-kaurane natural diterpenoid obtained from rabdosia rubescens . it acts by inhibiting the ATPase activity by forming covalent bonding with C279 and there by blocking the interaction between NLRP3 and NEK7[56] it is mainly useful in treatment of arthritis and Alzheimer's disease[36].

Dehydroisohispanolone [DIH]:it blocks the ATP binding site PDB7ALV by covalent bonding. It also form covalent bond with a cystine residue in the NACHT domine there by blocking the interaction between NEK7 and NLRP3 thus Preventing the activation by causing conformational change. It also act by inhibiting the caspase-1 activity in LPS-primed J774A and it also reduce the expression of GSDMD-N , thus reducing the pyroptosis. It is mainly useful in treating the inflammatory diseases[55].

INF4E: it is a α,β unsaturated cyano or carbonyl derivative. It inhibit NLRP3 by inhibiting the ATPase activity. It is may be useful in treating rhinosinusitis[37].

Parthenolide : it is a sesquiterpene lactone which is present in Tanacetum parthenium.it inhibit NLRP3 inflammasome activation by inhibiting the NF-kB signaling pathway. It also inhibit the ATPase activity[35, 37]. Synthesis of parthenolide derivative compounds which are less toxic like compound 8b play a key role in treating neuroinflammatory diseases[36].

Bay 11-7082; it is a phenyl vinyl sulphone identified as an NLRP3 inhibitor. It act by inhibiting the NF-kB signaling pathway[37] through interacting with IKkB kinase. It also act on the ATPase and inhibit the oligomerization of NLRP3 inflammasome[35] It is mainly useful in treating chronic inflammatory diseases , neuroinflammatory and Alzheimer's disease[36].

β hydroxy butyrate [BHB] : it is a ketone body produced by liver during the metabolism of fatty acids. It acts by inhibiting K^+ efflux and there reducing the oligomerization of NLRP3 inflammasome and speck formation of ASC[35]. It is mainly useful in treating chronic inflammatory diseases and Alzheimer's disease[35, 36]

F11A-2: it is also called 1-ethyl-5-methyl-2-phenyl -H benzo[d] imidazole. It acts by inhibiting autolytic cleavage of procaspase-I thus it will ultimately causes the inhibition of NLRP3 inflammasome activation, thus it may be useful in treating rhinosinusitis but it is not mentioned that it definitely cures rhinosinusitis[35].

Isoliquirtigenin :it is a phenolic compound obtained from licorice. It inhibit the NLRP3 inflammasome by acting on NrF2 signaling pathway through dependent and independent manner[35].

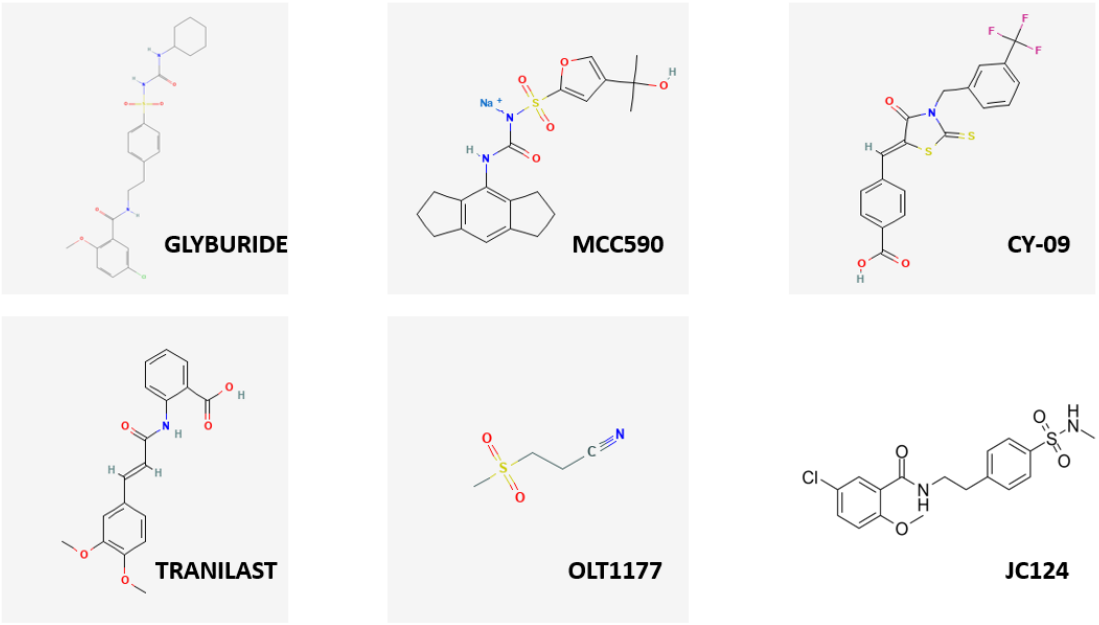

Fig.4. Structure of NLRP3 Inflammasome inhibiting agent.

Tablet format of various NLRP3 inhibitors and their method of action

S.NO	NLRP3 inhibitor	Method of acting	Outcome	refference
1.	Tranilast	Indirectly	Bind with NACHT region of NLRP3	[29]
2.	Bay 11-7082	Directly	By inhibiting the NLRP3 ATPase activity	[35]
3.	OLT117	Directly	By inhibiting the NLRP3 ATPase activity	[37, 49, 50]
4.	BHB	Indirectly	Inhibits the K+ efflux	[35]
5.	CY-90	Indirectly	By inhibiting the NLRP3 ATPase activity	[35]
6.	A740003	Indirectly	By inhibiting P2X7R binding with NLRP3	[29]
7.	FC11A-2	Indirectly	By inhibiting caspase-1 activation	[35]
8.	Micro RNA 133b	Indirectly	By inhibiting the expression of NLRP3	[54]
9.	Glyburide	Indirectly	By inhibiting K+ ATP sensitive channel	[35]
10.	isoliquiritigenin	Indirectly	By inhibiting the NF-kB pathway	[35]
11.	Deubiquitinases	Directly	By inhibiting ubiquitination of NLRP3	[30]
12.	JC124	Indirectly	By inhibiting the expression of NLRP3	[35]
13.	Oridonin	Directly	By inhibiting ATPase activity of NLRP3 [48]	[56]
14.	MCC950	Directly	By blocking the ATPase domine of the NLRP3	[35]
15	DIH	Indirectly	Binds to the NACHT domine of NLRP3	[55]
16.	MNS	Directly	By inhibiting the NLRP3 ATPase activity	[35]
17.	INF4E	Directly	By inhibiting the NLRP3 ATPase activity	[37]
18.	Parthenolide	Directly	By inhibiting the NLRP3 ATPase activity	[35]

NLRP3 INHIBITORS which are undergoing clinical trials

Drug name	Clinical trial	refference
OLT11779 (dapansutrile)	Phase -II [47, 53]	[37, 55]
IFM2427	Phase -I [47]	[55]
NT-0167	Phase -I [47]	[55]
Somalix	Phase -II [47]	[55]
Inzomelid	Phase -II [47]	[55]

VI. Conclusion

NLRP3 Inflammasome plays a significant role in the Rhinosinusitis progression due to its caspase producing activity. This caspase is responsible for the conversion of pro-inflammatory mediators to interleukins and further these interleukins are responsible for the progression of Inflammation in nasal and paranasal sinuses. However, the NF-KB signaling pathway is responsible for the activation of NLRP3 genes. DAMPs & PAMPs are the ligands which bind to the toll like receptors and elicit the response to NF-KB signaling molecules. Furthermore, evidences of research are in support of involvement of NLRP3 proteins in the Rhinosinusitis.

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Conflict of interest

The authors declare no conflict of interest.

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List of Abbreviations

NLRP3- NLR family Pyrin domain containing 3
NLR- NOD like Receptor
ASC- Apoptosis-associated speck-like Protein containing a CARD
IL- Interleukins
ATP- Adenosine triphosphate
RNA- Ribonucleic acid
NF-KB- Nuclear factor kappa light chain enhancer of activated b cells
CRWNP- Chronic Rhinosinusitis with nasal polyps
CRWONP- Chronic Rhinosinusitis without nasal polys
DPB- Diffuse pan Bronchiolitis.
PAMP- Pathogen associated molecular pattern
DAMP- Damage associated molecular pattern
MHC- Major Histocompatibility complex
PYD- Pyrin domain
NACHT- Conserved in NAIP, CIIT, HET-E and TP1
NMR- Nuclear magnetic resonance spectroscopy
CARD- Caspase activation recruitment domain
INF-γ – Interferon gamma
ILRs- Interleukin receptors
TNFR- Tumor necrosis factor receptor
TLR- Toll-Like receptor
CASP- Cytohesin-activated scaffolding protein

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