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Review article

Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in cytokine storm modulation

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ABSTRACT

The world has witnessed a high morbidity and mortality caused by SARS-CoV-2, and global death toll is still rising. Exaggerated inflammatory responses are thought to be more responsible for infiltrated immune cells accumulation, organ damage especially lung, dyspnea, and respiratory failure rather than direct effect of viral replication. IL-6 and NLRP3 inflammasome are the major immune components in immune responses stimulation upon pathogen infection. It's noteworthy that the function and expression of these components are remarkably influenced by non-coding RNAs including long non-coding RNAs. Given the potential role of these components in organ damage and pathological manifestations of patients infected with COVID-19, their blockage might be a hopeful and promising treatment strategy. Notably, more study on long non-coding RNAs involved in inflammatory responses could elevate the efficacy of anti-inflammatory therapy. In this review we discuss the potential impact of IL-6 and NLRP3 inflammasome blocker drugs on inflammatory responses, viral clearance, and pathological and clinical manifestations. Collectively, anti-inflammatory strategy might pave the way to diminish clinical and pathological manifestations and thereby discharging patients infected with COVID-19 from hospital.

1. Introduction

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly disseminate all around the world by 9,068,108 confirmed cases and 471,042 death until June, 22, 2020 [1]. COVID-19 is an enveloped virus that belongs to the *Coronaviridae* family containing a positive-sense RNA genome which encodes essential structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) [2]. COVID-19s' cell entry strongly depends on S protein through interacting with angiotensin-converting enzyme (ACE) on the target tissues such as lung, kidney, heart, and gastrointestinal (Fig. 1) [3,4]. The inflammatory cascade is activated following sensing virus' RNA and its structural proteins by inflammatory sensors [5,6]. It seems that interleukin-6 (IL-6) and NOD-like receptor protein 3 (NLRP3) inflammasome are the major cause of inflammatory cytokine storm, and thereby clinical and pathological manifestations of patients infected with COVID-19 [7,8]. Correspondingly, infiltrated immune cells including macrophages and monocytes, minimal lymphocytes including $CD4^+$ T cells, eosinophils and neutrophils were presented in lungs of patients who died of SARS-CoV-2 [9]. Its noteworthy that epigenetic modulations such as non-coding RNAs, DNA methylation, and histone acetylation are implicated in inflammatory cytokine storm and inflammatory complex including IL-6, tumor necrosis factor (TNF)-α, and NLRP3 inflammasome [10,11]. Therefore, designing anti-inflammatory drugs to target inflammatory cytokines especially IL-6 and inflammatory complex including inflammasome could be a promising strategy to deal with SARS-CoV-2 [12,13]. Patients with rheumatoid arthritis showed down-regulation of the levels of acute-phase reactants including prototypic C-reactive protein (CRP) upon administration of tocilizumab [14]. Also, glyburide is a food and drug administration (FDA) approved drug for treatment of type 2 diabetes able to block NLRP3 inflammasome activation through inhibiting ATP sensitive K^+ (KATP) channels, caspase-1, IL-1β, and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) assembly, thereby halts inflammation responses and organ damage [15–18]. Furthermore, well recognition of non-coding RNAs involved in SARS-CoV-2-induced inflammation response could serve as new prognostic biomarkers and therapeutic targets in treatment of patients infected with COVID-19 [10]. Collectively, co-administration of anti-IL-6 and inflammasome blocker drugs might improve clinical manifestations of

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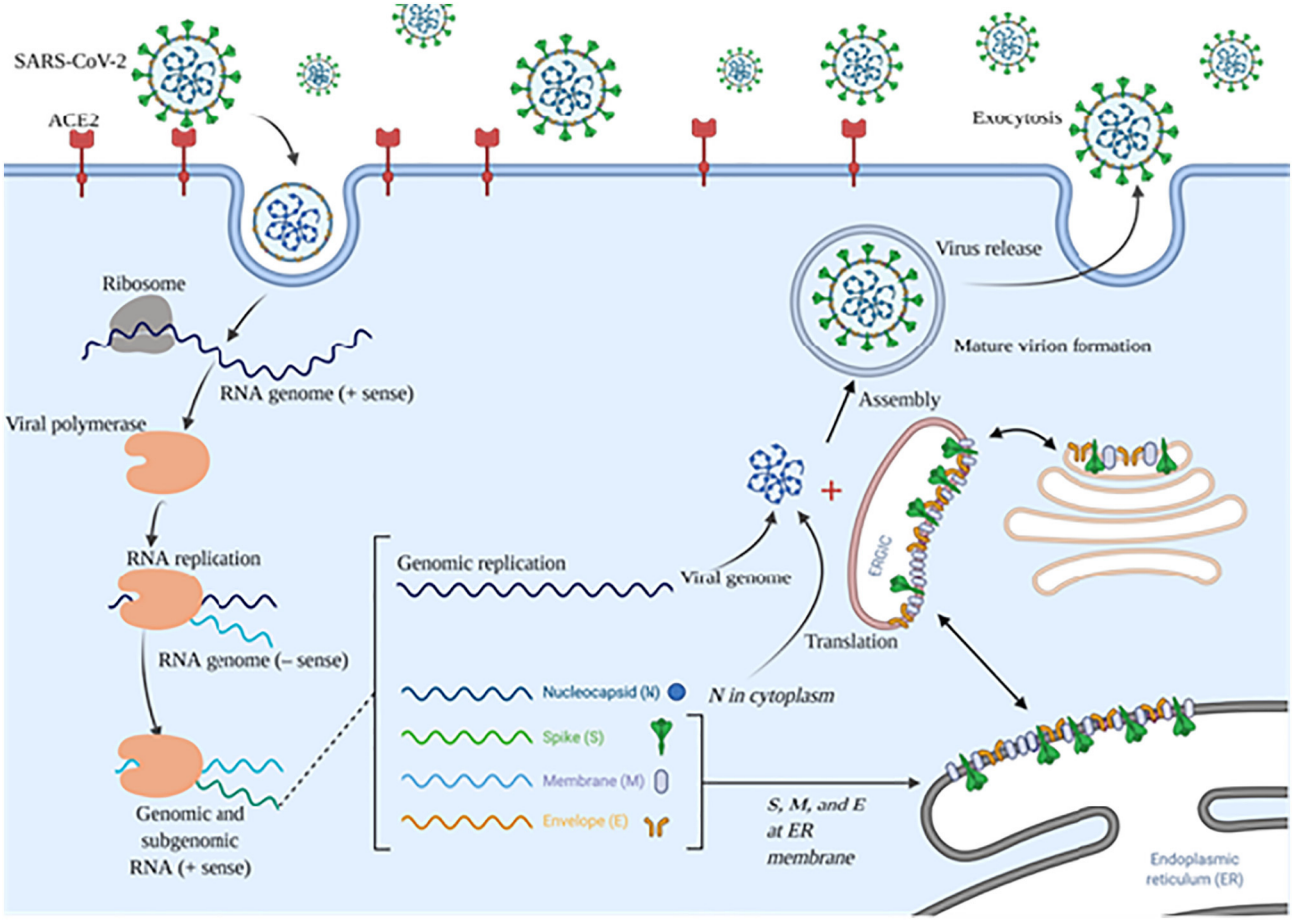


Fig. 1. The mechanism of cell entry and life cycle of SARS-CoV-2 in host cell; SARS-CoV-2 life cycle initiation is mediated by S protein binding to the ACE2. Conformation change in S protein following binding to ACE2 promotes its fusion with cell membrane via endosomal pathway. Viral genomic RNA is released and translated into viral polymerase proteins that synthesize the negative (−) sense genomic RNA, and thereby produce a series of subgenomic mRNAs to translation and residing of essential, structural viral proteins including nucleocapsid (N), spike (S), membrane (M), envelope (E) into ER and further transport to the Golgi apparatus. Finally, viral RNA–N complex and S, M, and E proteins are assembled into virion and released out of the host cell. ACE2: angiotensin-converting enzyme 2; ER: endoplasmic reticulum; ERGIC: ER–Golgi intermediate compartment.

COVID-19 patients, and reduce morbidity and mortality through limiting COVID-19-mediated inflammation responses. In this review, we describe the mechanism of IL-6 and NLRP3 inflammasome in pathogenesis of SARS-CoV-2, and thereby clinical and pathological manifestations of the disease. Also, we review long non-coding RNAs implicated in IL-6 and NLRP3 inflammasome activation. Finally, we discuss mechanism and pharmacokinetic properties of some reported pharmacological inhibitors targeting these most important inflammatory components.

2. Mechanism of IL-6 secretion and inflammatory cascade formation mediated by SARS-CoVs' infection

SARS-CoV-induced inflammatory responses largely cause organ damage especially lung, and thereby high mortality and morbidity [7,19]. Inflammatory cytokines comprising IL-6, and TNF-α and inflammatory complexes including inflammasome were activated following ACE-mediated SARS-CoVs' cell entry [20,21]. Studies carried out on human and animal models infected with SARS-CoV suggest that SARS-CoV-mediated fatal pneumonia might be due to immunopathological events [22–24]. Also, human lung fibroblasts infected with MERS-CoV and HCoV-229E were shown to cause a delayed, strong increase in the levels of IL-1β, IL-6, IL-8, TNF-α, interferon (IFN)-β, and IFN-γ-induced protein (IP)-10. However, the levels of IL-6, IL-8, IFN- β, and IP-10 were significantly higher in HCoV-229E-infected cells relative to MERS-CoV-infected cells [25]. Moreover, the lungs' pathological study of patients who died of COVID-19 demonstrated the presence of infiltrated immune cells such as macrophages and monocytes, minimal lymphocytes including $CD4^+$ T cells, eosinophils and neutrophils, alveolar exudative inflammation as well as interstitial inflammation (Fig. 2) [9]. Recent studies raised the possibility that inflammatory cytokine storm and inflammatory events may be responsible for the severe COVID-19 pathology [26,27].

2.1. IL-6 secretion mediated by SARS-CoVs' infection

IL-6 is a potent pro-inflammatory cytokine that plays a crucial role in inflammatory responses, autoimmune diseases, cancers, and viral infections [28]. Also, recently IL-6 have been identified in development of SARS-CoV-2-induced inflammatory responses, and further affected patient's clinical manifestations [29]. Relatively, recent studies illustrated the remarkable, higher levels of IL-6 in patients with COVID-19 in comparison with those in control group. Also, the levels of IL-6 were strongly correlated with severity of patients' clinical manifestation, serum SARS-CoV-2 viral load (RNAaemia), and mechanical ventilation requirement [14,30–32]. Moreover, the levels of IL-6 were increased up to 7-fold ($P = 0.016$) following human peripheral blood mononuclear cells (PBMCs) treatment with SARS-CoVs' spike protein through activation of nuclear factor kappa B (NF-κB) pathway [33]. Correspondingly, treatment of murine macrophages cell line (RAW264.7) with

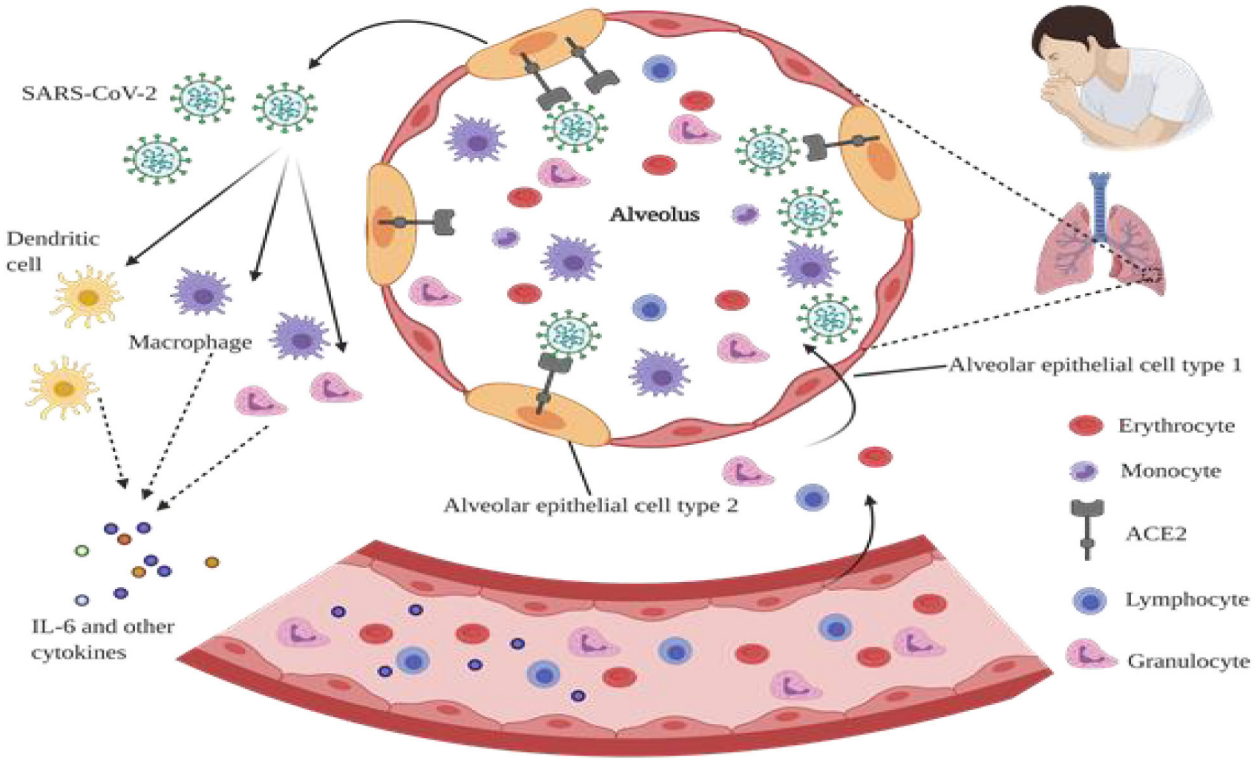


Fig. 2. Possible mechanism of cytokine release syndrome in severe COVID-19 patients. SARS-CoV-2 infects alveolar epithelial type 2 cells through ACE2 receptor, leading to destruction and permeability of epithelial cells, and thereby virus release. Releasing of virus strongly activates innate and adaptive immune cells including macrophages, granulocytes, lymphocytes, monocytes, dendritic cells, and also a large number of cytokines including IL-6. Furthermore, following the stimulation of inflammatory factors, a large number of inflammatory cells and erythrocytes enter the alveoli, and cause dyspnea and respiratory failure.

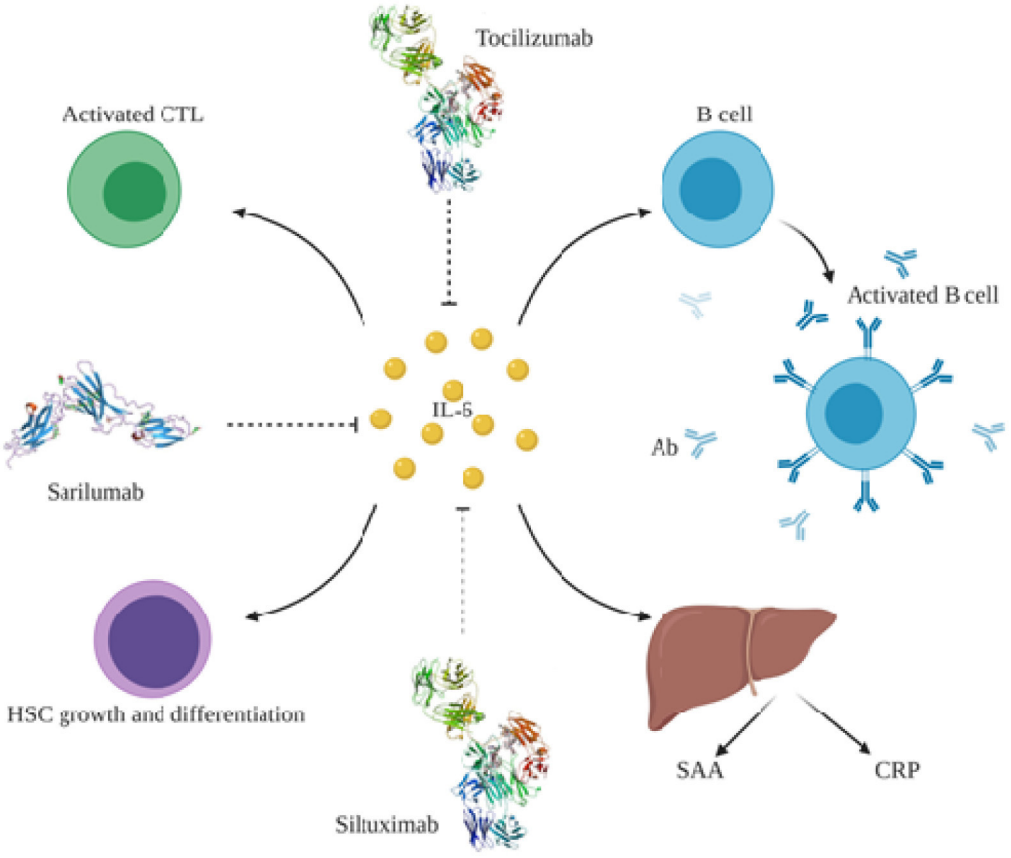


Fig. 3. IL-6 is involved in inflammation through activating different pathways. IL-6 influences both B and T lymphocyte cells to induce antibody production and CTL activation, respectively. IL-6 promotes HSC growth through enhancing the differentiation of blood cells and promoting their colony formation. Moreover, IL-6 influences acute phase reactive protein production such as SAA and CRP from hepatocytes. CTL: cytotoxic T lymphocyte; Ab: antibody; CRP: C-reactive protein; SAA: serum amyloid A, HSC: hematopoietic stem cells.

SARS-CoV spike protein led to NF-κB-induced IL-6 and TNF-α up-regulation [34]. IL-6 exerts its effects on target cells through three different mechanisms comprising binding directly to the membrane-bound glycoprotein 130 (gp130), also known as classical signal transduction; forming a complex with its receptor IL-6R and then binding to gp130; and binding to soluble gp130 in a trans presentation manner [35,36]. IL-6 influences immune processes via activating multiple downstream signaling pathways including janus kinase/signal transducers and activators of transcription (JAK-STATA) (STAT1,3, and 5) [37,38], RAS-rapidly accelerated fibrosarcoma (RAS-RAF) [37,39], SRC-yes-associated protein(YAP) -neurogenic locus notch homolog (NOTCH) [40], phosphatidylinositol 3-kinase (PI3K)-AKT [41,42]. IL-6 has a pivotal role in regulating the immune system and inflammatory pathways through several ways including promoting B lymphocytes proliferation and differentiation to induce antibody production (Fig. 3) [43], cytotoxic T lymphocyte (CTL) activating [44], inducing hepatocytes-mediated acute phase reactive proteins secretion [45], and hematopoietic stem cells differentiation [46]. Moreover, IL-6 could induce T helper-17 (Th-17) cells, is a pro-inflammatory cytokine involved in pathogenesis of several inflammatory diseases, via recruiting the transforming growth factor beta (TGF-β) [47,48]. It's noteworthy that IL-6 is also known as a major inducer of acute phase reactive protein that lead to acute phase reactive proteins secretion comprising serum amyloid A (SAA) and CRP from hepatocytes [45,49]. Recently, it was shown that IL-6 is a core regulator of vascular endothelial growth factor (VEGF) expression, and vessel permeability in alveolar epithelial cells [50,51].

2.2. NLRP3 inflammasome formation upon SARS-CoVs' infection

SARS-CoV-2 induces IL-1 family members including IL-1β and IL-18 through activating an inflammatory protein complex named NLRP3 inflammasome [21,52]. Activation of NLRP3 inflammasome occurs via two signaling mechanisms (Fig. 4). The first one also called priming signal is triggered via microbial agents sensing with toll like receptors (TLRs) or cytokines to NF-kB-induced pro-IL-1β and NLRP3 up-regulation. The second one is triggered by pathogen associated molecular patterns (PAMPs), and danger-associated molecular patterns (DAMPs) resulting in ASC and pro-caspase-1 assembly, and thereby activation of NLRP3 inflammasome [53,54]. Its noteworthy that NLRP3 inflammasome is also activated by ATP and K^+ efflux in a P2X7 receptor and pannexin-1 dependent manner [54]. Inflammasome is a central inflammatory multimeric complex including pro-caspase-1, ASC, and NLRP3 protein [55]. Inflammasome is activated via nucleotide-binding oligomerization domain–like receptors (NLRs) upon sensing a wide stimuli spectrum comprising PAMPs, DAMPs, and reactive oxygen species (ROS) [56,57]. Several types of NLRs, innate cytosolic receptors, including NLRP1–7, and NLRP12 could promote inflammasome assembly; nonetheless NLRP3 is more studied than other types [58,59]. Multiple lines of evidence illustrated that NLRP3 interacts with the pyrin domain (PYD) of ASC following sensing stimulus-mediated oligomerization, and then ASC recruits pro-caspase-1 via a caspase recruitment domain (CARD) [60]. Consequently, upon autocatalysis, activated caspase-1 cleaves pro-interleukin (IL)-1β and pro-IL-18 into IL-1β and IL-18 respectively, resulting in inflammatory responses [61]. Recent in vitro study have illustrated that SARS-Coronavirus open reading frame-8b interacts with leucine-rich repeat (LRR) domain of NLRP3 to activating NLRP3 inflammasome, leading to increasing levels of IL-1β and IL-18 in macrophages and probably lung epithelial cells [52]. Surprisingly, another recent study revealed that SARS-CoV open reading frame-3a protein activates both required signaling mechanisms to inflammasome activation independent of ion channel activity. Therefore, open reading frame-3a either activates NF-κB and thereby IL-1β transcription through inducing ubiquitination of p105 in a TRAF3-dependent manner, or it interacts with TRAF3 to induce K63-linked ubiquitination of ASC and consequently promotes caspase 1 activation and IL-1β maturation [62]. SARS-CoV 3a protein acts as a viroporin to NLRP3 inflammasome formation, and thereby IL-1β and IL-18 secretion through K^+ channel activity and mitochondrial ROS induction [63]. SARS-CoV E protein ion channel activity is associated to IL-1β secretion through acting as Ca^+ channel, and consequently forms NLRP3 inflammasome compartment [21]. Correspondingly, creation of N15A and V25F mutations in the transmembrane domain of SARS-CoV E protein abrogated the Ca^+ flux as well as K^+, Na^+, and Cl^- transportation [21,64]. Animals infected with SARS-CoV without E protein ion channel activity have shown decreased inflammasome-induced IL-1β highlighting the pivotal role of E protein in inflammasome formation. Consistently, mice infected with SARS-CoV containing E protein ion channel activity displayed swollen alveoli walls and leukocyte infiltration whereas those infected with SARS-CoV lacking E protein ion channel activity presented moderate swollen lung epithelia and leukocyte infiltration [64].

3. Role of LncRNAs implicated in IL-6 and NLRP3 inflammasome signaling pathway

LncRNAs are a novel class of non-coding transcripts with longer than 200 nucleotides length, and play a crucial role in a broad spectrum of disorders [65–67]. A growing number of studies have indicated that ncRNAs play a crucial role in inflammatory disease progression [68–70]. LncRNAs have been strongly implicated in regulation of NLRP3 inflammasome and IL-6-assocciated inflammatory signaling [10,71,72].

3.1. LncRNAs involved in IL-6 secretion

There is some evidence about the key role of lncRNAs in both down- and up-regulation of *IL-6* [10]. As listed in Table 1, and Fig. 5 lncRNAs may regulate *IL-6* expression via several pathways like JAK/STAT, NF-κB, HIF-1α, and MAPK. LncRNA/IL-6/STAT is one of the well-studied pathways involved in multiple malignancies such as gastric cancer, hepatocellular carcinoma, non-small cell lung cancer, etc. [73–75]. Correspondingly, lncRNA down-regulated in liver cancer stem cells (*lnc-DILC*) suppresses *IL-6* transcription and its downstream pathway, JAK2/STAT3, and also reduces spheroid formation by binding directly to *IL-6* promoter in *lnc-DILC* overexpressing cells. Moreover, subcutaneous inoculation of hepatoma cells knocked down for *lnc-DILC* to mice resulted in a greater xenograft tumor growth, size, and weight, highlighting the fundamental role of *lnc-DILC* in restraining liver cancer stem cells and hepatocellular carcinoma progression. Also, patients with higher levels of *lnc-DILC* showed a lower risk of hepatocellular carcinoma recurrence and better survival following surgical resection [76]. Another regulator lncRNA is tumor-suppressive lncRNA on chromosome 8p12 (*TSLNC8*) that remarkably suppresses proliferation, migration, invasion, and autophagy, and induces apoptosis in non-small cell lung cancer through inactivating IL-6/STAT3/hypoxia-inducible factor 1-alpha (HIF-1a) axis [77]. Contrary to *lnc-DILC* and *TSLNC8*, lncRNA regulating *IL-6* transcription (*LNRRIL6*) demonstrated an oncogenic role by promoting IL-6/STAT3 axis and its downstream molecules including cell division cycle 25 A (CDC25A), cyclin D1, survivin, and B-cell lymphoma 2 (BCL2). Relatively, injection of *LNRRIL6* overexpression cells into athymic nude mice induced tumor growth [78]. Strikingly, lncRNA metastasis associated lung adenocarcinoma transcript 1 (*MALAT1*), also known as *NEAT2*, has indicated a dual role regarding inflammation responses and cytokine secretion especially *IL-6* in different signaling pathways. Increased *MALAT1* levels induced by acute kidney injury and cobalt chloride-induced hypoxia in mice suggested that it might have an anti-inflammatory role in acute kidney injury. Also, knocking down *MALAT1* in HK2 cells led to NF-κB and HIF-1α activation, and consequent increase of many inflammatory cytokines such as IL-6 and TNF-a to promoting inflammatory cell infiltration and tissue damage [79]. Moreover, the inflammatory role of *MALAT1* has been revealed upon its overexpression, and thereby

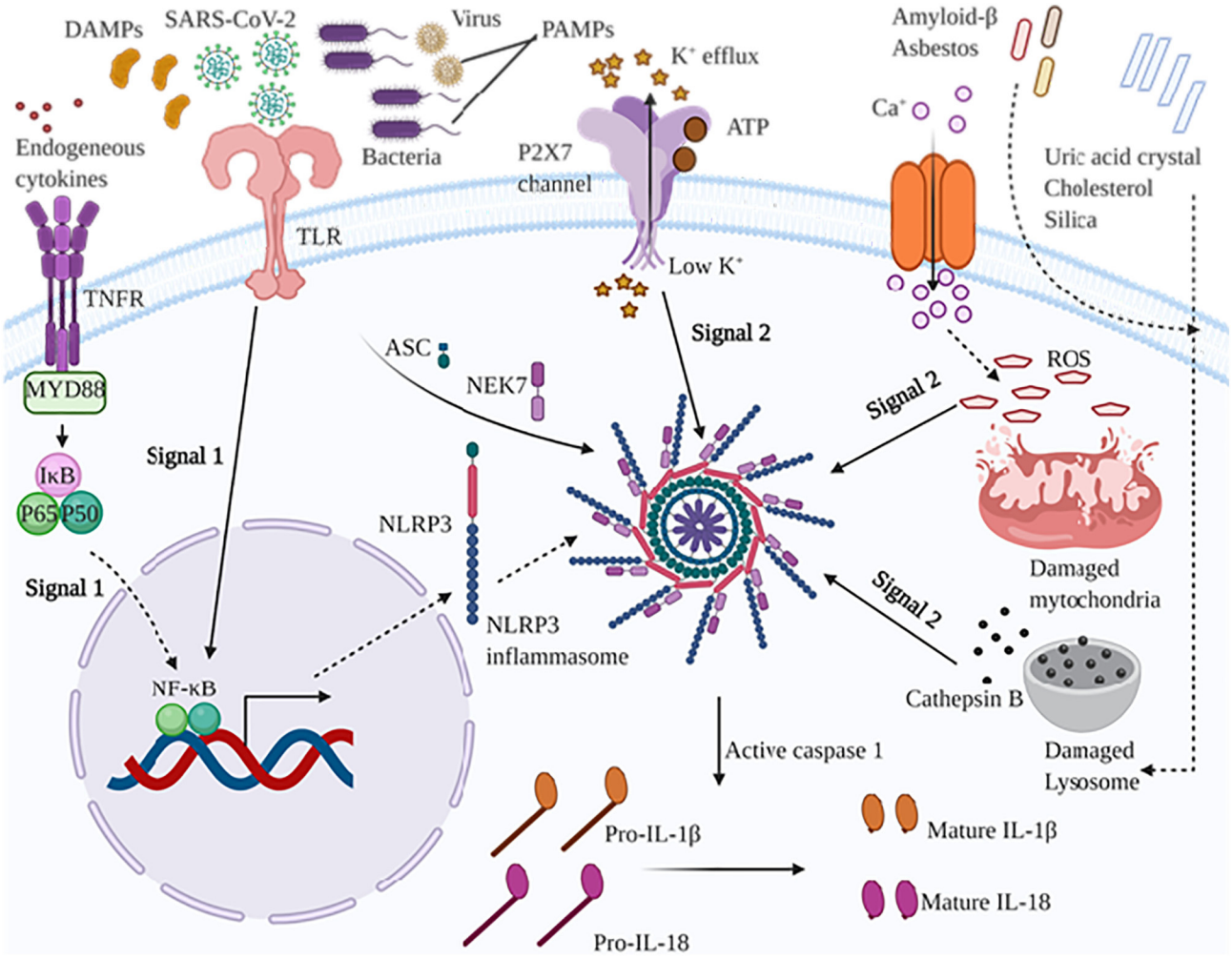


Fig. 4. NLRP3 inflammasome pathway is activated through signal 1 and signal 2. Signal 1 is mediated trough sensing microbial and virus ligands (PAMPs), DAMPS, and cytokines such as TNF-α by TLR and TNFR, respectively. Activation of signal 1 leads to NF-kB pathway activation, and thereby up-regulates pro-IL-1β, pro-IL-18, and NLRP3 protein levels. Signal 2 is primed by extracellular ATP and K^+ efflux leading to the activation of NLRP3 inflammasome via the P2X7 receptor. Also, calcium influx activates NLRP3 inflammasome by damaging mitochondria, and consequently releases the mitochondrial ROS. Different endogenous and exogenous agents including amyloid β, asbestos, uric acid crystal, cholesterol, silica crystal cause lysosome damage and cathepsin B release from lysosome into cytosol, promoting NLRP3 activation. Collectively, NLRP3 inflammasome activation leads to caspase 1 activation, and thereby converting pro-IL-1β and pro-IL-18 into mature form. TNFR: tumor necrosis factor receptor; TLR: toll-like receptors; DAMPs: damage-associated molecular patterns; PAMPs: pathogen associated molecular patterns; IκB: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; P2X7: P2X purinoceptor 7; IL: interleukin.

inflammatory cytokines (*IL-6, TNF-α, and IL-1β*) up-regulation in LPS-induced acute lung injury. Correspondingly, histopathological investigation of the lung sections of *MALAT1* knocked down rat demonstrated that LPS-induced lung injury was strongly diminished in comparison with the control group [80]. Furthermore, *IL-6* up-regulation was shown to be tightly linked to T-cell proliferation blockage, accumulation of infiltration neutrophils in ovarian cancer tissue, and ovarian tumor growth through recruitment by lncRNA *HOXA* transcript at the distal tip (*HOTTIP*). In view of these, NOD/SCID mice were injected by *HOTTIP* overexpressing SKOV3 cells demonstrated a higher tumor volume in comparison with those injected with normal SKOV3 cells [81]. Surprisingly, IL-6 was shown to be also regulated through NF-κB signaling following HOX antisense intergenic RNA (*HOTAIR*)-mediated nuclear translocation and activation of NF-κB in LPS-induced macrophages. In the light of this result, the levels of inflammatory response and cytokines induced by LPS potentially decreased upon *HOTAIR* knock down in RAW264.7 cells [82]. Another oncogenic lncRNA that might be implicated in inflammatory cytokines regulation including *IL-6, IL-1β,* and *TNF-α,* and consequently neuropathic pain development in chronic constriction injury (CCI) rats model is lncRNA nuclear-enriched abundant transcript 1 (*NEAT1*). Consistently, neuropathic pain has ameliorated in *NEAT1* knocked down rat upon considerable down-regulation of inflammatory cytokines such as IL-6, IL-1β, and TNF-α which suggested the crucial role of *NEAT1* in regulation of *IL-6* expression [83]. Current studies regarding osteoarthritis pathogenesis suggest that lncRNA cardiac autophagy inhibitory factor (*CAIF*) could restrain osteoarthritis progression through blocking *miR-1246*, and IL-6. Also, it was shown that the IL-6 and *miR-1246* levels were remarkably up-regulated in synovial fluid of osteoarthritis patients whereas *CAIF* was significantly down-regulated, highlighting the potential role of IL-6 in osteoarthritis as an inflammatory disease [84].

3.2. LncRNAs implicated in NLRP3 inflammasome formation

Inflammasome, a multiprotein complex, is a core inflammatory component involved in innate immunity and inflammation responses upon induction with various stimuli [89]. Accumulating evidence has indicated that lncRNAs are implicated in inflammasome formation followed by severe disorders promotion (Table 2, Fig. 5) [72,90]. Nuclear enriched abundant transcript 1 (*NEAT1*) has been associated with

Table 1
Most relevant lncRNAs involved in dysregulated IL-6 signaling pathway and their target molecules.

LncRNA	Target(s)	Tissue or cell type	Effect	Disease	References
DILC	IL-6/STAT	Liver cancer stem cells (in vitro) and tumor xenografts in mice	Suppresses IL-6 expression, spheroid formation, and JAK2/STAT3 signaling	Hepatocellular carcinoma	[76]
TSLNC8	IL-6/STAT3/HIF-1a	A549 cells	Inhibits proliferation, migration, invasion, and autophagy and induces apoptosis	Non-small cell lung cancer	[77]
LNRRIL6	IL-6/STAT3	Colorectal cancer tissue (in vitro) and athymic nude mice (in vivo)	Promotes CRC cell survival and tumor growth	Colorectal cancer cells	[78]
UICC	IL-6/STAT3	Caski, SiHa, HeLa, Ms751 and C33a cells (in vitro) and xenograft tumors grown from HeLa cells overexpressing lnc-UICC (in vivo)	Promotes tumor growth and metastasis	Cervical cancer	[85]
MALAT1	NF-κB and MAPK pathways	Acute lung injury rats (in vivo) and rat pulmonary microvascular endothelial cells (in vitro)	Induces inflammatory responses and cytokine release including IL-6 and TNF-α	Acute lung injury	[86]
MALAT1	NF-κB/HIF-1α/IL-6	Acute kidney injury mice (in vivo) and HK2 cells (in vitro)	Anti-inflammatory effect	Acute kidney injury	[79]
MALAT1	miR-146-a	LPC-induced acute lung injury rats (in vivo)	Induces inflammatory responses and cytokine release including IL-6 and TNF-α	Acute kidney injury	[80]
HOTTIP	STAT3/PD-L1	NOD/SCID mice (in vivo) and ovarian cancer cells (in vitro)	Promotes inflammatory responses	Ovarian cancer cells	[81]
HOTAIR	NF-κB	LPS-induced macrophages (in vitro)	Inflammatory response and cytokines release	Inflammation	[82]
NEAT1	miR-381/HMGB1	Chronic constriction injury rats (in vivo)	Neuropathic pain development	Chronic constriction injury	[83]
CAIF	miR-1246/IL-6	Synovial fluid and CHON-001 cells (in vitro)	Promotes inflammatory responses	Osteoarthritis	[84]
MEG3	miR-203	LPS-induced ATDC5 cells injury (in vitro)	Promotes inflammatory injury	Osteoarthritis	[87]
PVT1	TNF-α/JNK NF-κB pathway	LPS-induced HK-2 cells	Promote inflammatory response	Septic acute kidney injury	[88]

malignancy in multiple types of cancer including non-small cell lung, ovarian, cervical, and breast cancer suggesting its potential role in cell proliferation and tumor growth [91]. Moreover, murine immortalized bone marrow-derived macrophages (iBMDMs) induced by LPS facilitated *NEAT1* translocation from nucleus to the cytoplasm to inflammasome assembly, and thereby caspase 1 activation and inflammatory cytokine release, highlighting the inflammatory role of *NEAT1*. Accordingly, treatment of *Neat1* knocked out mice ($Neat^{-/-}$) with LPS resulted in reduced caspase 1 activation and IL-1β secretion in comparison with wild type mice ($Neat^{+/+}$). Surprisingly, hypoxia-induced iBMDMs indicated that *Nlrp3*, *Nlrc4*, and absent in melanoma 2 (*Aim2*) up-regulation are triggered by Hif-1α which might be mediated by Hif-2α-induced *Neat1* up-regulation [92]. Intriguingly, antisense non-coding RNA in the INK4 locus (*ANRIL*) has been closely linked to inflammation responses through acting as a competing endogenous RNA (ceRNA). *ANRIL* up-regulates the BRCA1-BRCA2-containing complex subunit 3 (BRCC3) and NLRP3 inflammasome, and consequently promotes uric acid nephropathy by sponging *miR-122-5p*. In this regard, histological study of kidney section of *Anril* knocked down rat indicated that the inflammatory cells infiltration, collagen fibers, and renal injury were more prominent than those in control group. Also, HK-2 cells transfected with *ANRIL* showed that NLRP3, IL-1β, and IL-18 were remarkably up-regulated whereas siRNA-medicated *ANRIL* silencing in HK-2 cells showed that *NLRP3*, *IL-1β*, and *IL-18* were suppressed [93]. One of the tumor suppressive lncRNAs that is down-regulated in a wide variety of cancers is lncRNA growth arrest-specific transcript 5 (*GAS5*) [94]. In this context, inducing *GAS5* overexpression in nude mice with ovarian cancer led to tumor growth inhibition via promoting ASC and caspase 3 expression to activation of inflammasome, and further increasing IL-1β secretion. Also, *GAS5* knock down in 3AO cell line demonstrated that *GAS5* exerts its antitumor activity via inflammasome-induced inflammatory cytokine release [95]. Another lncRNA that serves as a tumor suppressor in a NLRP3 inhibition manner is *XLOC_000647* that is implicated in pancreatic cancer pathogenesis. Correspondingly, subcutaneous injection of pancreatic cancer cell lines including MIA-PaCa-2 and BxPC-3 expressing *XLOC_000647* into nude mice resulted in significantly lower tumor weight in comparison with control group [96]. Long intergenic noncoding RNA (LincRNA)-*Gm4419* is another regulatory lncRNA related to inflammation events through NF-κB pathway. *Gm4419* facilitates inflammation in diabetic nephropathy through NF-κB-mediated NLRP3 inflammasome activation by binding to p50 (NF-κB subunit), in a positive feedback manner. Also, *Gm4419* knock down in mesangial cells with high glucose expression resulted in inflammation, fibrosis, and proliferation down-regulation whereas *Gm4419* overexpression with low glucose reversed these phenotypes [71].

4. IL-6 and NLRP3 inflammasome blocker drugs are promising strategy to combat COVID-19

High morbidity and mortality caused by current SARS-CoV-2 pandemy created an urgent need for developing effective therapeutic strategies to combat SARS-CoV-2 pathogenesis and thereby its outbreak [1]. Accumulating evidence suggest that the inflammatory cytokine storm and inflammatory responses might be responsible for the severe COVID-19 pathology and clinical manifestation deterioration [27,99]. Accordingly, recent studies carried out on patients infected with COVID19 showed that inflammatory cytokines including IL-1β, IL-18, IL-6, and TNF-α were remarkably higher in comparison with subjects in control group [30,33,100]. Also, there is some evidence about the potential role of NLRP3 inflammasome in SARS-CoV-induced inflammatory cytokine responses modulation [21,63]. The probable role of inflammatory cytokines especially IL-6 and NLRP3 inflammasome in SARS-CoV-2 pathogenesis have raised the possibility that blockage of inflammatory cytokines and NLRP3 inflammasome might be a hopeful strategy to cope with COVID-19 [101]. Previous studies have indicated

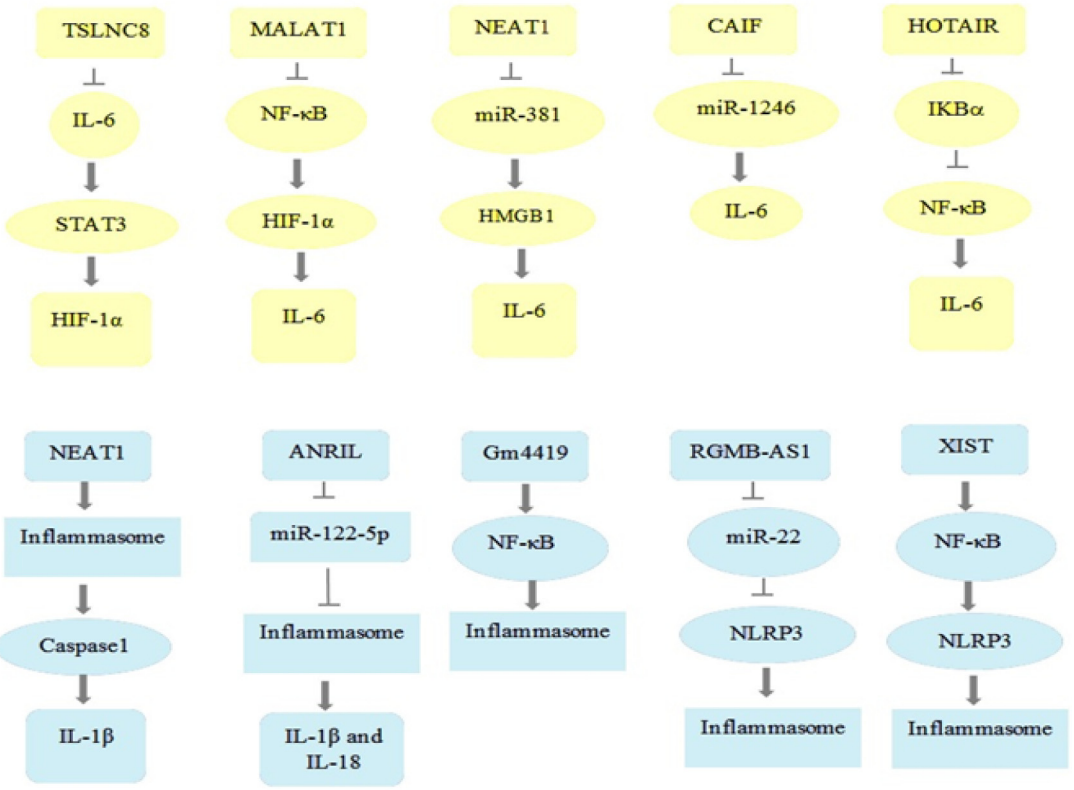


Fig. 5. Different potential lncRNAs and their targets involved in IL-6 and NLRP3 inflammasome pathway. IL: interleukin; STAT: signal transducers and activators of transcription; HIF-1α: hypoxia-inducible factor 1-alpha; IκB-α: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NACHT, LRR, and PYD domains-containing protein 3.

the efficiency of several anti-NLRP3 inflammasome and anti-cytokine small molecules in management of inflammatory, and autoinflammatory diseases [18,102].

4.1. IL-6 blocker drugs

Elevated plasma levels of inflammatory cytokines especially IL-6 in patients infected by SARS-CoV-2 shed some light on efficacy of therapeutic strategy of IL-6 blockers in ameliorating of severe clinical manifestations induced by SARS-CoV-2 infectious [14,29] (Fig. 3, Tables 3, 4). Tocilizumab, a humanized monoclonal antibody also known as actemra, inhibited the IL-6 receptor (IL-6R), and thereby significantly decreased serum acute phase reactants such as CRP, and SAA in patients who were injected intravenously with 2, 4, or 8 mg/kg biweekly for 6 weeks [103–105]. Given the indirect inhibitory mechanism of tocilizumab through abrogating IL-6 signaling by binding to its receptor, unbound IL-6 serum levels are increased after initial drug administration but are gradually down-regulated upon immune activation abrogation [105,106]. Notably, after several clinical trial studies intravenous administration of tocilizumab was approved in Japan (2008), Europe (2009), and USA (2010) and further subcutaneous injection was also approved in USA (2013) and in Europe (2014) [107,108]. BML-111, a lipoxin receptor agonist, has an anti-inflammatory effect through several mechanisms. BML-111 potentially decreases TNF-α, inflammatory cells infiltration, NF-κB/DNA binding activity, and P65 nuclear translocation whereas it promotes IκB-α expression and consequently suppresses inflammation in rats with haemorrhagic shock-induced acute lung injury [109]. It also can alleviate inflammatory responses and inflammatory cells infiltration in acute lung injury by blocking MAPK/AP-1 pathways and interfering with IL-6, IL-8, AP-1/DNA interaction [110]. In this view, BML-111 was shown to cause a significant increase in *MALAT1* levels which is down-regulated in rats with acute lung injury, and consequently *MALAT1* reduces activation of NF-κB, MAPK, and expression of inflammatory factors including monocyte chemoattractant protein-1 (MCP-1) and IL-6 [86,109].

4.2. NLRP3 inflammasome blockers

A growing body of evidence highlit the potential role of inflammatory components such as NLRP3 inflammasome in inflammatory responses mediated by SARS-CoV-2's infection. Correspondingly, it's becoming increasingly evident that anti-NLRP3 inflammasome drugs could diminish the inflammatory responses, and consequently alleviate clinical manifestations of patients with inflammatory disorders [111–113] (Fig. 6, Tables 3, 4). Glyburide, also known as glibenclamide, have been long used for type 2 diabetes treatment by blocking ATP sensitive K^+ (KATP) channels [16,17]. It potentially could inhibit caspase-1 and IL-1β activation following treatment of human trophoblasts with nigericin [15]. It also partially prevents ASC complex from aggregation, but doesn't show any effect on NLRC4 or NLRP1 [18]. Furthermore, glyburide impedes PAMP, DAMP, and crystal-mediated NLRP3 inflammasome activation in bone marrow-derived macrophages [114]. MCC950 is another small molecule that inhibits both canonical and non-canonical NLRP3 inflammasome activation through interacting with a wide spectrum of components. Moreover, treating of bone marrow-derived macrophages with MCC950 caused inhibition of IL-1β secretion through abrogating of caspase-1 [18] or disrupting ASC oligomerization [18]. It's noteworthy that MCC950 blocks ATP hydrolysis ability of NLRP3, an essential process to activation of inflammasome, by direct binding to Walker B motif located in NLRP3 NACHT domain [115]. Notably, MCC950 couldn't influence NLRC4, AIM2, and NLRP3 or TLR signaling [18]. OLT1177 is a β-sulfonyl nitrile drug which is being investigated under phase II

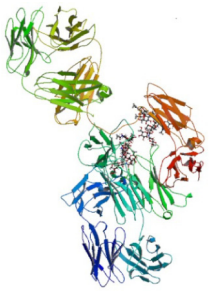
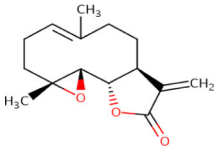
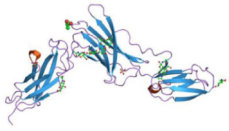
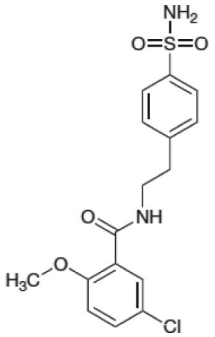
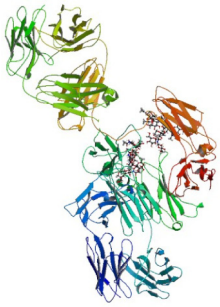
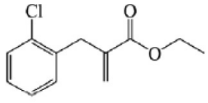
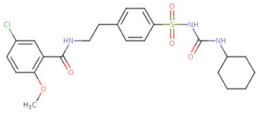
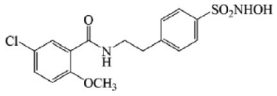
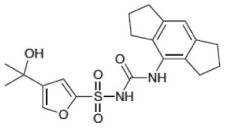
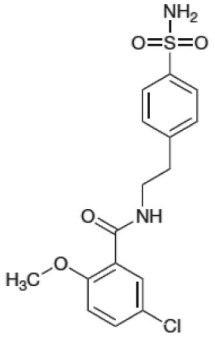
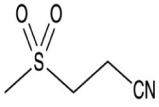
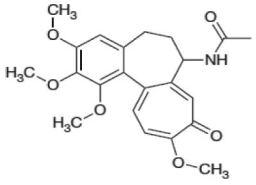
Table 2
Most relevant lncRNAs involved in dysregulated NLRP3 inflammasome signaling pathway and their target molecules.

LncRNA	Target(s)	Tissue or cell type	Effect	Disease	References
NEAT 1	Caspase1	LPS-induced murine immortalized bone marrow-derived macrophages (in vitro) and mice treated with LPS	Inflammasome activation and IL-β secretion	Inflammation	[92]
ANRIL	miR-122-5p/BRCC3	Kidney section of rat and HK-2 cells	Uric acid nephropathy and inflammation responses	Uric acid nephropathy	[93]
GAS5	ASC and Caspase3	Nude mice with ovarian cancer (in vivo) and 3AO cell line	Suppresses ovarian cancer	Ovarian cancer	[95]
GAS5	NLRP3	Cardiac fibrosis induced in Sprague-Dawley rats (in vivo) and cardiac fibroblast tissue (in vitro)	Inhibits cardiac fibrosis	Cardiac fibrosis	[11]
XLOC_000647	NLRP3	Nude mice	Suppresses pancreatic cancer	Pancreatic cancer	[96]
Gm4419	NF-κB	Mesangial cells	Promotes inflammation in diabetic nephropathy	Diabetic nephropathy	[71]
RGMB-AS1	miR-22/NLRP3	Hep-2 and AMC-HN-8 cells (in vitro) and tumor xenograft in nude mice (in vitro)	Tumor growth and poor prognosis	Laryngeal squamous cell carcinoma	[97]
XIST	NF-κB/NLRP3 inflammasome	Mammary alveolar cell-T (MAC-T) infected with E. coli and *S. aureus*	Promotes cell proliferation, viability and apoptosis of inflammatory MAC-T	Inflammation in bovine mammary epithelial cells	[98]

Table 3
Potential mechanisms of several IL-6 and NLRP3 inflammasome inhibitors.

Agent	Target (s)	Potential mechanism	Disease	References
Tocilizumab	Interleukin-6 receptor	Inhibits interleukin-6 receptor consequently decreased serum acute phase reactants such as CRP, and SAA	Rheumatoid arthritis	[103,105]
Sarilumab	Interleukin-6 receptor	Inhibits interleukin-6 receptor consequently decreased serum acute phase reactants such as CRP	Rheumatoid arthritis	[118]
Siltuximab	Interleukin-6 receptor	Inhibits interleukin-6 receptor consequently decreased serum acute phase reactants such as CRP and circulating free IL-6	Metastatic renal cell cancer	[119]
BML-111	Interleukin-6 receptor	-Upregulates lncRNA MALAT levels to decreases reduced activation of NF-κB, MAPK, and IL-6 -Disrupts IL-6, IL-8, AP-1/DNA interaction -Inhibits NF-κB and suppresses inflammatory responses	Acute lung injury	[86] [110] [109]
Glyburide	NLRP3 (indirect)	Blocks ATP sensitive K+ (KATP) channels, inhibits capase-1, disrupts ASC complex forming	Inflammatory disease	[15,17,18]
MCC950	NLRP3	Inhibits caspase-1, ASC oligomerization, blocks the ATPase domain of NLRP3, and thereby inhibits of canonical and non-canonical NLRP3 inflammasome activation	Inflammation, Parkinson's	[18,115,120]
OLT1177	NLRP3	Disrupts in recruiting of ASC and caspase-1 by NLRP3 and blocks NLRP3 inflammasome activation	Cryopyrin-associated periodic syndrome	[117]
Fc11a-2	NLRP3	Suppresses TNF-a, IL-1β, IL-18, IL17A and IFN-g	Dextran sulfate sodium-induced model of experimental colitis in mice	[121]
BOT-4-one	NLRP3	Impairs ATPase activity of NLRP3 by alkylation of NLRP3	Peritonitis in mice	[122]
Parthenolide	NLRP3	Inhibits ATPase activity of the NLRP3 inflammasome via alkylation of NLRP3, inhibits NF-κB, phosho-p38MAPK, and caspase-1	Rat stroke model	[102,123]
BAY 11-7082	NLRP3	Inhibits ATPase activity of the NLRP3 inflammasome independent of their NF-κB inhibitory activity.	Rat stroke model	[102,123]
INF39	NLRP3	Inhibits ATPase activity of NLRP3	Colitis in rat	[124]
JC-171	NLRP3	Inhibits NLRP3 activation and IL-1β secretion	Multiple sclerosis	[125]
16673-34-0	NLRP3	Inhibits NLRP3 inflammasome formation	Myocardial injury following ischemia-reperfusion in the mouse	[126]
Colchicine	NLRP3 (indirect)	Prevents NLRP3 assembly through blocking of ASC oligomerization, lysosome damage and P2X7 receptor activity	Acute myocardial infarction in mouse model	[127]
AZD9056	NLRP3 (indirect)	P2X7 inhibitor	Rheumatoid arthritis	[128]
GSK1070806	IL-18	Inhibition of IL-18	Type 2 diabetes mellitus	[129]
Canakinumab	IL-1β	INHIBITS IL-1β	Lung cancer	[130]

Table 4
Three dimensional or chemical structure of most effective IL-6 and NLRP3 inflammasome blockers.

Name	Chemical or 3D structure	Name	Chemical or 3D structure
Tocilizumab		Parthenolide	
Sarilumab		BAY 11-7082	
Siltuximab		INF39	 IFN-39
Glyburide		JC-171	
MCC950		16673-34-0	
OLT1177		Colchicine	

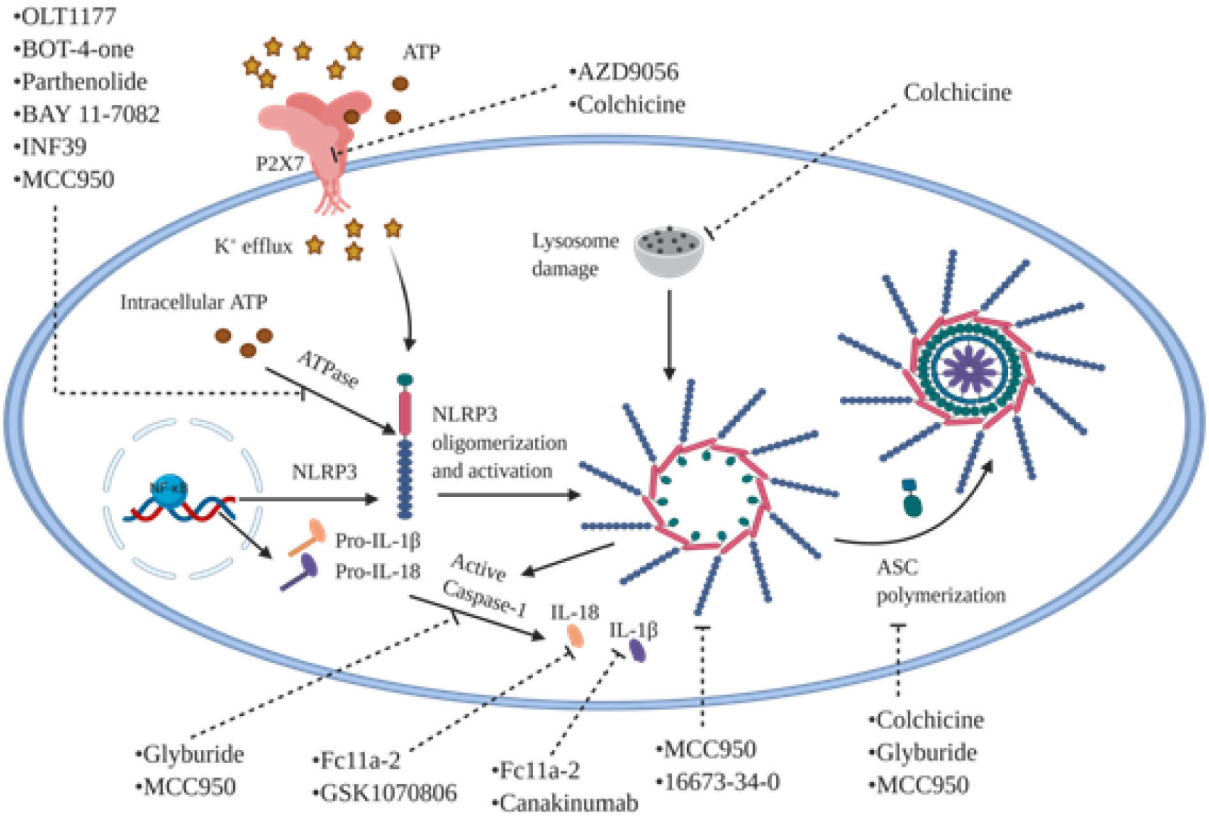


Fig. 6. Mechanism of action of most potential pharmacological inhibitors for NLRP3 inflammasome blockage. Several chemical agents have been studied with inhibitory effects on different component of NLRP3 inflammasome pathway. OLT1177, BOT-4-one, parthenolide, BAY 11-7082, INF39, and MCC950 could inhibit ATPase activity of NLRP3. MCC950 and 16673-34-0 are able to inhibit NLRP3 oligomerization. Colchicine, glyburide, and MCC950 block NLRP3 inflammasome activation through disruption of ASC oligomerization. Colchicine could also halt lysosome damage and P2X7 receptor activity as well as AZD9056, consequently prevents from NLRP3 inflammasome activation. GSK1070806 similar to Fc11a-2 suppress IL-18 secretion whereas canakinumab as well as Fc11a-2 block IL-1β. NLRP3, NACHT, LRR, and PYD domains-containing protein 3; P2X7, P2X purinoceptor 7; IL: interleukin; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain.

clinical trial for the treatment of acute gouty arthritis [116]. In this regard, murine macrophages cell line J774A.1 treated with OLT1177 was shown to cause 50% decrease of IL-1β secretion induced by LPS/ATP stimulation. However, the IL-1β and IL-18 secretion were diminished by 60% and 70%, respectively following human monocyte derived macrophages treatment with OLT1177. Also, it reduced IL-1β secretion via disrupting ASC and caspase-1 recruitment by NLRP3, thereby blocking NLRP3 inflammasome formation. However, OLT1177 doesn't have any effect on NLRC4, AIM2, TNF-α, and ion flux. It's noteworthy that OLT1177 also decreased IL-6 by 44% in mice with LPS-induced systemic inflammation [117]. Taken together, anti-inflammatory agents raise hope for diminishing pathological and clinical manifestations, and consequently morbidity and mortality induced by SARA-CoV-2 through targeting the main components involved in cytokine storm including IL-6 and NLRP3 inflammasome.

5. Discussion

The ongoing high morbidity and mortality caused by SARS-CoV-2s' pandemy pose a threat to global public health. SARS-CoV-2 outbreak has generated an urgent requirement to highly efficient with low side effect agents to combat it [131]. Recent studies have shown that exaggerated inflammatory responses and inflammatory cytokine storm might be the main cause of COVID-19 pathogenesis, and thereby fatality [27,99,132]. The potential role of IL-6 and NLRP3 inflammasome in immune response upon SARS-CoV-2 infection have emerged the hypothesis that blocking of these components could be a hopeful strategy to cope with it [14,20,21,133]. However, concerns have been raised about the probable role of epigenetic modulations including DNA methylation, histone modification, and ncRNAs such as micro RNA, lncRNA, and circular RNA (circRNA) in controlling IL-6 and inflammasome expression [10,134]. Therefore, designing and administration of potential drugs to target the wide spectrum molecules involved in IL-6 and inflammasome-associated epigenetic mechanisms along with IL-6 and inflammasome blockers may improve the efficacy of SARS-CoV-2s' treatment [12,13]. On the other hand, some of these ncRNAs have an anti-inflammatory effect through blocking IL-6 and inflammasome components whereas others promote inflammatory responses [77,135]. Recently, it was reported that circRNA_100782, as an oncogene, promotes pancreatic ductal adenocarcinoma BxPC3 cells proliferation by counteracting inhibitory effects of miR-124 in IL6-JAK2-STAT3 signaling pathway. Correspondingly, circRNA_100782 knocked down BxPC3 cells injected into BALB/c nude mice suppressed cell growth and IL6/STAT3 signaling pathway [136]. Contrary, circulating circ-DLGAP4 has an anti-inflammatory effect through sponging miR-143, and consequently decreases significantly CRP as well as inflammation cytokines including serum TNF-α, IL-6, IL-8 and IL-22 without affecting ESR, IL-1β, and IL-17 serum levels [137]. Furthermore, down-regulated miR-149 in osteoarthritis chondrocytes, exacerbates osteoarthritis progression via increasing inflammatory cytokines including TNF-α, IL-6, and IL-1β [138]. Notably, *GAS5* is widely down-regulated by epigenetic mechanisms resulting in tumor progression in various malignancies [94]. Also, *GAS5* down-regulation following DNMT1-mediated methylation of its promoter promotes pyroptosis-related proteins caspase1 and NLRP3 up-regulation, and thereby cardiac fibrosis progression. In this view, inducing cardiac fibrosis in rats led to

Gas5 down-regulation and *Nlrp3*, caspase1, and *Dnmt1* up-regulation [11]. Besides, some anti-inflammatory agents including emodin exert their effect via recruiting ncRNAs. Emodin, suppresses LPS-induced murines' ATDC5 cells apoptosis and inflammation by up-regulating lncRNA taurine-upregulated gene 1(*Tug1*), and thereby blocks NF-κB signaling and inflammatory cytokines especially Il-6 [139]. Discrepant results from several clinical trials about the efficacy of antiviral drugs including lopinavir/ritonavir (LPV/r) or arbidol in restraining COVID-19 infection and patients' manifestations raise the possibility that the pathological and clinical manifestations of infected patients might be due to virus-induced inflammatory cytokine storm and not only to virus replication [140]. Obtained results from a clinical trial including administration of tocilizumab for 20 patients with acute COVID-19 showed that 19 patients recovered from hospital within two weeks [141]. Tiziana Life Sciences (TZLS-501) is another fully-human anti-IL6R monoclonal antibody able to bind to both the membrane-bound and soluble forms of IL-6R, and thereby reduces circulating IL-6 levels in the blood and lung damage [142]. TJM2, a neutralizing antibody, is a promising agent to treatment of SARS-CoV-2 patients through targeting human granulocyte-macrophage colony stimulating factor (GM-CSF), and consequently diminishes inflammatory cytokine storm [141]. Furthermore, glyburide might be a useful drug to combat SARS-CoV-2 through blocking the wide spectrum of molecules related to inflammatory cascade including KATP channels, ASC oligomerization, caspase-1 and IL-1β, and it also could inhibit PAMP, DAMP, and crystal-mediated NLRP3 inflammasome activation [15–18]. Strikingly, lungs' pathological postmortem examination of SARS-CoV-2 patients have shown elevated infiltrating immune cells including macrophages and monocytes, minimal lymphocytes including $CD4^+$ T cells, eosinophils, and neutrophils, highlighting the probable role of inflammatory cells in deterioration of patients' clinical manifestations [9]. Correspondingly, elevated IL-6 serum levels in patients infected with SARS-CoV-2 suggested that the IL-6 serum levels is remarkably associated with severity of patients' clinical manifestations, serum SARS-CoV-2 viral load (RNAaemia), and mechanical ventilation requirement [14,30–32]. Moreover, results from recent studies shed some light on the importance of IL-6 serum levels as a diagnostic and prognostic biomarker in patients infected with SARS-CoV-2 [30,143]. Taken together, it seems that antiviral drugs and anti-inflammatory agent's co-administration might be more efficient to reducing SARS-CoV-2 patient's clinical manifestations and inflammatory responses-induced organ damage. Further clinical trials should be performed to evaluate the efficiency and safety of anti-inflammatory agents targeting IL-6 and NLRP-inflammasome and also, identify COVID-19 patients that may benefit from anti-inflammatory therapy.

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Declaration of competing interest

Authors declare no conflict of interest.

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