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Aggravating mechanisms from COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces immune-mediated diseases. The pathophysiology of COVID-19 uses the following three mechanisms: (1) inflammasome activation mechanism; (2) cGAS–STING signaling mechanism; and (3) SAMHD1 tetramerization mechanism, which leads to IFN-I production. Interactions between the host and virus govern induction, resulting in multiorgan impacts. The NLRP3 with cGAS–STING constitutes the primary immune response. The expression of SARS-CoV-2 ORF3a, NSP6, NSP7, and NSP8 blocks innate immune activation and facilitates virus replication by targeting the RIG-I/MDA5, TRIF, and cGAS–STING signaling. SAMHD1 has a target motif for CDK1 to protect virion assembly, threonine 592 to modulate a catalytically active tetramer, and antiviral IFN responses to block retroviral infection. Plastic and allosteric nucleic acid binding of SAMHD1 modulates the antiretroviral activity of SAMHD1. Therefore, inflammasome activation, cGAS–STING signaling, and SAMHD1 tetramerization explain acute kidney injury, hepatic, cardiac, neurological, and gastrointestinal injury of COVID-19. It might be necessary to effectively block the pathological courses of diverse diseases.

Highlights

1. DNA-driven immune response connects with NLRP3 and controls its inflammasome activity, which leads to IFN-I production via STING. The NLRP3 with cGAS-STING constitutes the primary immune response.
2. The expression of SARS-CoV-2 ORF3a, NSP6, NSP7, and NSP8 blocks innate immune activation and facilitates virus replication by targeting the RIG-I/MDA5, TRIF, and cGAS-STING signaling.
3. Plastic and allosteric nucleic acid binding of SAMHD1 reduces the magnitude of IFN and induction of virus-specific cytotoxic T cells. SAMHD1-deficient cells detect and activate IFN-I-mediated self ISG gene expression via cGAS–STING.
4. SAMHD1 autonomously controls viral infection through innate and adaptive immunity at the level of the infected cell.

Keywords CGAS–STING, Inflammasome, NLRP3, SAMHD1, SARS-CoV-2, COVID-19

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces immune-mediated diseases. They play important roles in the infectivity and pathogenesis of chronic diseases, including cancer, coagulation disorders, neurodegenerative disorders, and cardiovascular diseases. SARS-CoV-2 can stimulate pathological intracellular signaling pathways by triggering transcription factors, which play important roles in the progression of neurodegenerative diseases, epilepsy, multiple sclerosis, and multiple cancers, such as glioblastoma, lung malignancies, and leukemias [1]. These diseases are distributed across multiple geographical limits. Interactions between the host and virus govern induction, resulting in various consequences [2]. Blood levels of cytokines during infection with coronavirus disease 2019 (COVID-19) are characterized by distinct C-reactive protein (CRP), interleukin-6 (IL-6), or triglyceride levels and significantly increased circulation [3–7].

The NLR family pyrin domain containing-3 (NLRP3) inflammasome contains 1. NLRP3 is a sensor protein; 2. Apoptosis-associated speck-like protein with the caspase recruitment domain (ASC) as an adaptor protein, and 3. Caspase-1 is an effector protein [8].

1. The NLRP3 protein has three domains: ① the pyrin domain (PYD), ② the nucleotide-binding domain, and ③ the leucine-rich repeat domain. PYD interacts with ASC [8].
2. The ASC platform induces caspase-1 activation, which catalyzes the conversion of pro- interleukin 1β (IL-1β) to mature IL-1β. Excessive IL-1β activates various signaling pathways, such as the NF-κB and Jun N-terminal kinase (JNK) signaling pathways, and as a result, it stimulates systemic inflammatory responses. Interferon-α (IFN-α), interferon- β (IFN-β), IL-6, tumor necrosis factor (TNF), and TGFβ1 can lead to cytokine storms [8].
3. Caspase-1 is the most direct marker of inflammasome activation, and processes the inflammatory cytokines pro-IL-1β and pro-interleukin-18 (IL-18) into their biologically active forms, IL-1β and IL-18. Caspase-1 cleaves gasdermin D to generate pore-forming N-terminal fragments to induce cell pyroptosis by oligomerizing with and targeting the plasma membrane [9].

SARS-CoV-2 activates the cytosolic DNA (cDNA) sensor, cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) (cGAS–STING) signaling in endothelial cells. The cGAS–STING pathway controls immunity to cDNA and drives aberrant IFN-I responses in patients with COVID-19 [10]. The useful cellular functions of cGAS–STING are mediated by canonical and a few noncanonical pathways, but dysfunction of cGAS–STING-mediated cellular functions and noncanonical signaling underlie disease pathogenesis [11]. Severe COVID-19-related inflammation is associated with excessive lung tissue damage and syncytial pneumocyte formation. Cultured epithelial cells expressing ACE2 and the SARS-CoV-2 spike protein (SP) formed multinucleated syncytial cells. The fused cells exhibited DNA damage and micronuclei expressing cGAS–STING, which colocalized with and stimulated IFNs and IFN-stimulated genes [12].

The sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein 1 (SAMHD1) is a deoxyribonucleotide triphosphate triphosphohydrolase (dNTPase) that cleaves deoxynucleotide triphosphates (dNTPs) to deoxynucleosides and triphosphates. SAMHD1 operates at stalled replication forks to prevent the induction of IFN, a significant regulator of dNTP concentrations in human cells [13]. High dNTP levels can cause problems in maintaining mitochondrial function, which might occur in Aicardi–Goutières syndrome (AGS) patients [14]. AGS mutations in the SAMHD1 gene reduce catalytic activity or allosteric activation by dGTP and increase intracellular dNTP levels [15]. This genetic inflammatory encephalopathy resembles congenital viral infections and certain autoimmune disorders [16]. SAMHD1 mutations could lead to a more robust viral infection because of the loss of the dNTP triphosphohydrolase activity of SAMHD1 [17]. Viruses can replicate their viral genome with their polymerase.

Results

Inflammasome activation mechanism

The SARS-CoV-2 genome is enclosed by a nucleocapsid (N) protein in phospholipid bilayers. The membrane and envelope proteins are located among the SP in the virus envelope. There are four main types of inflammasomes, NLRP1, NLRP3, NLR family CARD domain containing 4 (NLRC4), and absent in melanoma 2 (AIM2), which are classified after being regarded as distinct sensing proteins. Inflammasomes consist of at least three components: the inflammasome caspase (caspase-1, caspase-4/11), an adapter molecule (ASC), and a sensor/receptor protein (NLRP1, NLRP3, NAIP1/2/5, NLRP12, AIM2, etc.) [8].

Active NLRP3 was detected in tissues and peripheral blood mononuclear cells (PBMCs) from postmortem patients with moderate or severe COVID-19. The serum levels of IL-6, lactate dehydrogenase (LDH), caspase-1, caspase-4/11, and IL-18 are correlated with disease severity [18]. SARS-CoV-2 engages in Caspase 4/11-mediated noncanonical activation of NLRP3 and

contributes to COVID-19 exacerbation [19]. Moreover, higher Caspase-1, Caspase-4/11, and IL-18 levels are associated with poor clinical outcomes [18, 19].

The N protein facilitated ASC oligomerization by increasing the interaction between NLRP3 and ASC. The N protein, NLRP3, and ASC form a complex and activate NLRP3. The N protein triggered A549 cells to release more serum cytokines than did SP and amplified NLRP3 activation and trimethylamine N-oxide (TMAO)-induced lipogenesis [20–22].

SP triggers the priming and activation of NLRP3 resulting in mature IL-1β formation in both cell types and the production of coagulation factors such as von Willebrand factor (vWF), factor VIII or tissue factor in human umbilical vein endothelial cells and monocytes [23]. Monocytes are differentiated by SARS-CoV-2 spike protein subunit 1 (S1), not the N protein. Monocytes exposed to S1 induced significantly greater proportions of T helper type 1 (Th1) and T helper type 17 (Th17) CD4 + T cells. CD4 + IFN-producing Th1 cells play a role in the induction of tissue inflammation and many organ-specific autoimmune diseases. Th17 cells are highly differentiated by specific cytokines, are auto pathogenic, can induce tissue inflammation, and are characterized by a unique cytokine signature [24]. An increase in Th1 and Th17 cells was observed in patients with COPD compared with current smokers without COPD and healthy subjects. The increase in the Th17 response and the loss of balance between CD4 + T-cell subsets in COPD patients contribute to a lack of regulation of the systemic inflammatory response [25]. Pyroptosis by SARS-CoV-2 is associated with caspase-1, caspase-4/11, IL-1β, and gasdermin D expression and cytokine levels in primary monocytes [19, 26] (Table 1).

SP induces neuroinflammation in BV-2 microglia and TLR4 expression is increased when BV-2 microglia, a microglial cell line derived from C57BL/6 mice, are simulated with S1. The purified SP activated NLRP3 in lipopolysaccharide (LPS)-primed microglia in an ACE2-dependent manner. Microglial NLRP3 activation is a major driver of neurodegeneration [50–54] (Table 2).

AIM2 senses potentially dangerous cytoplasmic DNA and cytosolic DNA (cDNA) triggers the formation of the AIM2 inflammasome by inducing AIM2 oligomerization. It leads to the activation of the ASC pyroptosome and caspase-1 [86]. The detection of cDNA via the cGAS–STING axis induces a cell death program that initiates potassium efflux upstream of NLRP3. The combination of NLRP3 with cGAS–STING constitutes the primary inflammasome response during viral and bacterial infections in human myeloid cells and ameliorates the pathology of inflammatory conditions linked with cDNA sensing [87]. Mitochondrial antiviral signaling protein (MAVS) connects with NLRP3 and controls its inflammasome activity [27].

cGAS–STING signaling mechanism

This cGAS–STING mechanism induces microglial activation to resolve inflammation in the brain. However, excessive engagement can lead to neuroinflammation and neurodegeneration [37]. cGAS–STING signaling is strongly related to the pathogenesis of neuroinflammation-driven disease progression [88]. Due to cellular senescence, autoimmune disorders, and mitotic stress in cancers, cytosolic DNA levels increase, and a vast array of germline-encoded innate immune receptors facilitate innate immune recognition. These lead to the activation of cGAS–STING and the exacerbation of pathological mechanisms [88, 89].

cGAS catalyzes the conversion of cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) to cDNA. It triggers STING–TANK binding kinase 1 (TBK1)—IFN regulatory factor 3 (IRF3) signaling [90]. cGAS also appears in the nucleus, where cGAS in an inactive state is isolated from chromatin. Upon viral infection, nuclear cGAS recruits protein arginine methyltransferase 5 (PRMT5). In innate immunity, nucleus-localized cGAS interacts with PRMT5 to catalyze the symmetric demethylation of histone H3 arginine 2 at IRF3-responsive genes, such as IFNβ 1 (IFNβ1) and IFNα 4 (IFNα4). As a result, PRMT5 facilitates IRF3 access [91]. Activated cGAS releases cGAMP, which binds to STING; thus, STING relocalizes and forms a clustered platform at the perinuclear Golgi. The kinase TBK1 phosphorylates IRF3, and IRF3 then enters the nucleus. Moreover, NF-κB triggers the expression of IFN-1 and proinflammatory cytokine genes [32, 35].

The papain-like proteases (PLpros) have deubiquitinase activities that enable human-infecting coronaviruses to evade innate defenses. PLpro suppressed antiviral signaling in cells by deubiquitinating the stimulator of STING [92]. Activated STING triggers membrane permeabilization and thus lysosomal cell death [87]. The SARS-CoV-2 ORF3a can interact with STING. It selectively blocks cGAS–STING-induced autophagy by disrupting the STING-light chain 3 (LC3) interaction [93].

SARS-CoV-2 nonstructural protein 6 (NSP6) promotes the degradation of macroautophagy/autophagy-mediated STING1 and inhibits IFN production [94]. ORF9b, nonstructural protein 7 (NSP7), and nonstructural protein 8 (NSP8) antagonize the production of IFN-I and IFN-III by targeting retinoic acid-inducible gene I (RIG-I)/melanoma differentiation-associated gene 5 (MDA5), toll-like receptor 3 (TLR3)-interleukin-1 receptor (TIR)-domain-containing adapter-inducing IFN-β (TRIF), and cGAS–STING signaling. The expression of ORF3a, NSP6, NSP7,

Table 1 The signaling and aggravating mechanisms of COVID-19

Classification	Mechanism	Signaling pathways	Viral Pathogenesis
1. Inflammasome activation pathway	Active caspase-1 is formed by autocatalytic cleavage, which then catalyzes the proteolytic processing of pro-[1]IL-1β into mature IL-1β and pro-IL-18 to produce mature IL-1β and IL-18. Excessive IL-1β stimulates systemic inflammatory responses [8, 27–29]	Activating various signaling pathways, such as the [2]NF-κB and [3]c-Jun N-terminal kinase P38 kinases mediate inflammasome activation [8, 20, 27, 28, 30]	[3]NLRP3 deubiquitylation and self-aggregation occur during NLRP3 inflammasome activation, followed by ASC recruitment and oligomerization. [4]N protein promoted the interaction between NLRP3 and [5]ASC. Inhibition of [6]Dpp8/9 and reduction of cytosolic ATP [20, 27, 30, 31]
2. cGAS–STING signaling pathway	A significant nucleic acid recognition pathway [32]. [6]cGAS is activated upon binding to aberrant DNA [33] Activated cGAS then synthesizes [7]cGAMP, a secondary messenger that activates the [8]STING gene [33, 34]	cGAS catalyzes the production of cGAMP upon sensing cytosolic DNA, which activates STING–[9]BK1–[10]IRF3 signaling. cGAS in the nucleus recruits [11]PRMT5, which facilitates IRF3 access upon viral infection [34, 35] Porcrine STING signaling exerts an IFN-independent antiviral, and its function are independent of both IFN and autophagy, and activates cell apoptosis independently of IFN and autophagy, and the apoptosis is associated with antiviral activity. STING antiviral activity includes IFN production, (NF-κB expression, autophagy, and apoptosis [36]	cGAS–STING signaling is strongly linked to the pathogenesis of CNS diseases that are underlined by neuroinflammation-driven disease progression [37–41]
3. SAMHD1 tetramerization pathway	SAMHD1 prevents chronic inflammation in cancer development: [12]CLL [42], a congenital inflammatory disease: [13]AGS [13, 14]. SAMHD1 acts as a HIV restriction factor [43] and hepato-cerebral mtDNA depletion syndrome in humans [44]	SAMHD1 forms tetramer structure of GTP and all four [14]dNTPs [42] and is engaged in the control of the dNTP pool, which contains a target motif for [15]CDK1 ([592]TPQK[595]) in the cell division cycle [45]. CDK1 activity is required for SAMHD1 phosphorylation, which on residue T[592] makes SAMHD1 not to block retroviral infection [45, 46]. SAMHD1 may function as a dNTPase to decrease intracellular dNTP pool and degrade retroviral RNA or viral DNA products generated in the infected cell [46]. SAMHD1 limits the release of single-stranded DNA from stalled replication forks and preventing cGAS–STING pathway to induce expression of pro-inflammatory IFN-I[13]. Unstable four allosteric sites make tetramerization dangerous and block the cytosolic DNA-sensing pathway. Genetic mutations of [16]dGK inside mitochondria can cause [17]mtDNA depletion in noncycling cells: when SANHD1 in the nucleus degrades endogenous dGTP, dGK inside mitochondria has recycled the deoxyguanosine [44]	SAMHD1 reduced the induction of virus-specific cytotoxic T cells [47]. [18]Vpx carries out several functions during infection, including the downregulation of SAMHD1 [48, 49]

[1] IL (Interleukin), [2]NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), [3]NLRP3 (NLR family PYRIN domain containing-3), [4]N protein (SARS-CoV-2 nucleocapsid protein), [5]ASC (Apoptosis-associated speck-like protein containing a CARD), [6]Dpp8 (Dipeptidyl Peptidase 8), [6]cGAS (Cyclic GMP-AMP Synthase), [7]cGAMP (cyclic guanosine monophosphate-adenosine monophosphate), [8]STING (stimulator of interferon gene), [9]TBK1 (tank-binding kinase 1), [10]IRF3 (interferon regulatory factor 3), [11]PRMT5 (protein arginine methyltransferase 5), [12]CLL (chronic lymphocytic leukemia), [13]AGS (Aicardi-Goutières syndrome), [14]dNTP (deoxynucleoside triphosphate), [15]CDK1 (cyclin-dependent kinase 1), [16]dGK (deoxyguanosine kinase), [17]mt (mitochondrial), [18]Vpx (Viral protein X)

Table 2 Three pathways basically implicated and associated with SARS-CoV-2 [188]

Classification	Mechanism	Signaling pathways	Viral Pathogenesis
1. ACE2 and TLR pathway	[1]S-protein has been proposed to have the most substantial protein—protein interaction with TLR4 [55–60]	[2]TLR2 and TLR4 are expressed intracellularly in dendritic, epithelial, and endothelial cells. TLRs in modulation of COVID-19 cytokine storm signaling in SARS-CoV-2 [50, 60–63]	Neurological symptoms induced by TLRs or S-protein [50, 59–61, 63]. Clinically evident or exacerbated with viral diseases or aging [64, 65]
2. Neuropilin-1 pathway	[3]NRP1 acts as a host cell mediator that can increase SARS-CoV-2 infectivity and contribute to its tissue/organ tropism [66–68]	NRPs are associated with numerous signaling pathways: [4]VEGF [68], [5]EGF [69], [6]FGF [70], [7]HGF [71, 72], [8]IGF [73], [9]PDGF [74, 75], [10]TGFβ [76], and [11]DPP-4 [77]	NRP-1 functions as a coreceptor for VEGF, HGF, PDGF, EGF, FGF, IGF, TGFβ, and DPP4, functionally involved in the migration and invasion of various cells, membrane disorders, angiogenesis as a hub receptor in the vascular system [78]
3. Spike protein pathway	The interaction of [12]ACE2–TLRs with SARS-CoV-2 S-protein in human [13]VSELs and [14]HSCs activates the NLRP3 inflammasome [57, 62, 79–81]	S-protein activates the NLRP3 Inflammasome and ACE2 is expressed on very small CD45 – precursors of hematopoietic and endothelial Cells and in Response to NLRP3 inflammasome with distinct epigenetic and gene expression signatures [82]	[15]PF4 dependent syndrome [16]AESI [81, 83–85]

[1] S-protein (SARS-CoV-2 Spike protein), [2]TLR4 (Toll-Like Receptor 4), [3]NRP1 (Neuropilin 1), [4]VEGF (Vascular Endothelial Growth Factor), [5]EGF (Epidermal Growth Factor), [6]FGF (Fibroblast Growth Factor), [7]HGF (Hepatocyte Growth Factor), [8]IGF (Insulin-Like Growth Factor), [9]PGGF (Platelet-Derived Growth Factor), [10]TGFβ (Transforming growth factor-β), [11]DPP-4 (Dipeptidyl peptidase 4), [12]ACE2 (Angiotensin Converting Enzyme 2), [13]VSEL (Very small numbers of embryonic-like stem cells), [14]HSC (hematopoietic stem cell), [15]PF4 (pathogenic platelet factor 4), [16]AESI (Adverse Event of Special Interest)

and NSP8 blocks innate immune activation and facilitates virus replication [93–98]. Mitochondrial DNA is released and leads to IFN-I production. Blocking STING reduces severe lung inflammation [10, 27, 99] (Fig. 1).

SAMHD1 tetramerization mechanism

SAMHD1 forms tetramers of GTP and all four dNTPs are controlled by the combined action and inactive apo-SAMHD1 interconverts between monomers and dimers through dGTP-induced tetramerization of two inactive dimers. The protein assembles into catalytically active tetramers in the presence of dGTP [100]. The binding of dGTP to four allosteric sites stimulates and causes a conformational change in the substrate-binding pocket, which results in a catalytically active tetramer [100]. A phosphomimetic environment generates electrostatic repulsive movement. This repulsive electrostatic phosphorylation allosterically decreases dNTPase activity and may modify antiviral functions [42].

When SANHD1 in the nucleus degrades endogenous dGTP, deoxyguanosine kinase (dGK) inside mitochondria is recycled from deoxyguanosine. Genetic mutations of dGK inside mitochondria can cause mtDNA depletion in noncycling cells: hepato-cerebral mtDNA depletion syndrome in humans [44]. However, phosphorylation of SAMHD1 at residue threonine 592 (T^{592}) modulates the ability of SAMHD1 to block retroviral infection [45].

SAMHD1 can restrict retroviruses and protect cells from viral infections by catalyzing the hydrolysis of dNTPs in the dNTP pool. SAMHD1 depletes intracellular dNTPs into 20-deoxynucleoside and triphosphate products [43, 45]. Cyclin-dependent kinases (CDKs) are protein kinases that play key roles in cell division, transcriptional regulation, and viral infections [101]. SARS-CoV-2 infection triggers and redistributes cyclin D1 and D3 from the nucleus to the cytoplasm and subsequent proteasomal degradation [102]. Cyclin D3 prevents the efficient incorporation of the envelope protein into virions during assembly. Its degradation during SARS-CoV-2 infection relieves cyclin interference with virion assembly [102].

SAMHD1 has a target motif for cyclin-dependent kinase 1 (CDK1, ^{592}TPQK^{595}) [45]. CDK1 activity is required for SAMHD1 phosphorylation. SAMHD1 phosphorylated at residue T^{592} does not block retroviral infection, but it does not affect the ability of SAMHD1 to decrease the cellular dNTP level [45].

Single-gene recessive inborn errors can result in uncontrolled inflammatory cytokine production by mononuclear phagocytes after SARS-CoV-2 infection, potentially explaining the origins of multisystem inflammatory syndrome in some children [16]. SAMHD1 mutations result in autoinflammatory AGS. AGS secretes chronic IFN-I despite the absence of viral infections [14, 15, 103]. The degradation of SAMHD1 in human primary-activated/dividing CD4 + T cells contributes to the increase in dNTP levels [104]. Plastic and allosteric nucleic acid binding promotes the immunomodulatory effects of the antiretroviral activity of SAMHD1 [105]. Phosphorylation modulates the ability of SAMHD1 as an HIV restriction factor to block retroviral infection without affecting its ability to decrease cellular dNTP levels [43], but SAMHD1-depleted cells release single-stranded DNA fragments from stalled forks and accumulate DNA fragments in the cytosol, where they activate reverse transcription, cGAS and STING, and signaling through the IFN receptor to induce the expression of proinflammatory IFN-I [13].

SAMHD1 autonomously controls viral infection through innate and adaptive immunity at the level of the infected cell and limits virus-induced production of IFNs and the induction of costimulatory markers: virus-induced IFN production in myeloid cells. SAMHD1 reduces the magnitude of IFN and the induction of virus-specific cytotoxic T cells [106]. The SAMHD1 tetramer structure could provide a mechanistic understanding of its rapid function in SARS-CoV-2 pathogenesis. SAMHD1-deficient cells detect and activate IFN-I-mediated antiviral gene expression in SAMHD1 KO cells via cGAS–STING [107]. SAMHD1 links with MAVS and suppresses MAVS aggregation in response to viral infection, which increases the phosphorylation of TBK1, an inhibitor of NF-κB kinase epsilon (IKKε), and IRF3 [108]. It inhibits NF-κB activation and IFN-I induction in response to viral infection [47, 109]. The antiviral IFN responses induced by SAMHD1 suppress SARS-CoV-2 replication and increase cellular innate immunity, but genetic loss of SAMHD1 increases the innate immune response and IFN activation [109]. Low levels of IFN-I could drive more severe SARS-CoV-2 infection [110]. SAMHD1 occurs more frequently in severe ventilation-associated COVID-19 patients than in nonventilated patients [111]. SAMHD1 regulates the innate immune response and adaptive IFN activation [34, 112]. Further research is still needed for the management of COVID-19 to study the regulatory functions of SAMHD1.

Limitations

Too many complex and diverse pathways are involved in IFN, making it difficult to find treatments that can effectively and efficiently manage it [112]. Because of the rapid and lethal nature of these three deterioration pathways, research to explain their interrelationships remains limited.

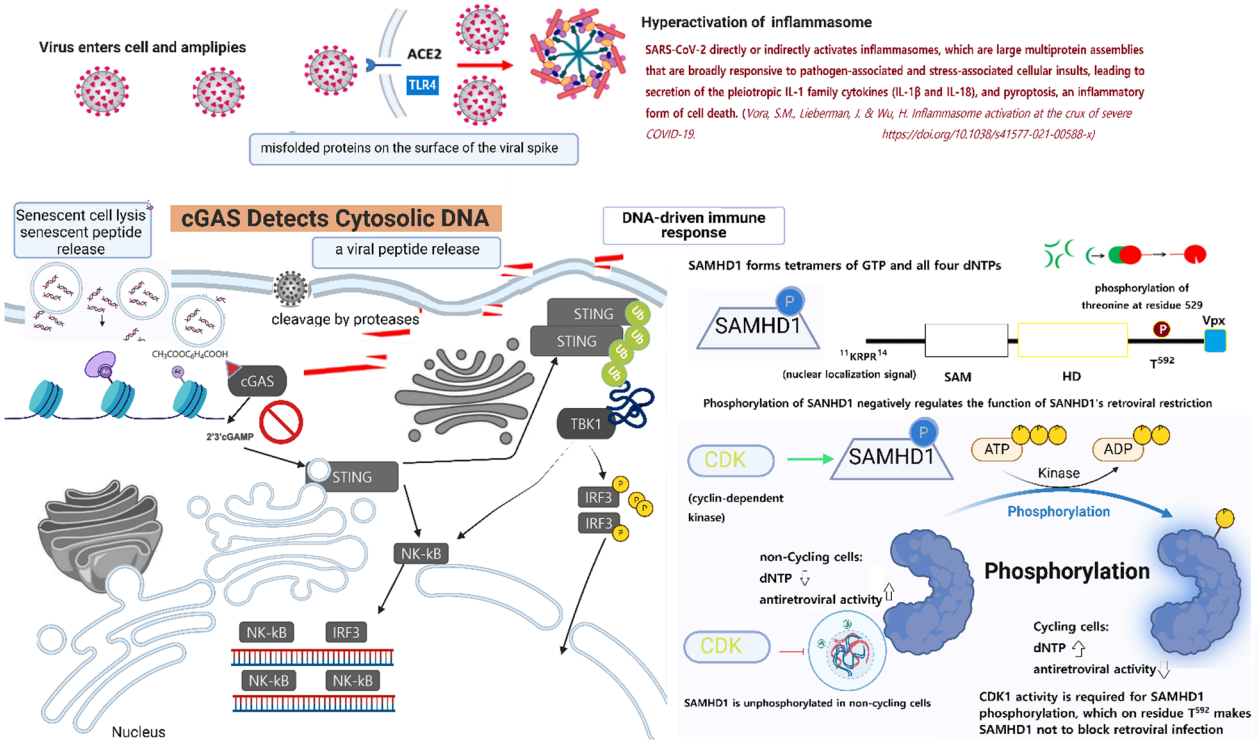

Fig. 1 Activation of Inflammasome, cGAS–STING, and SAMHD1. Angiotensin-converting enzyme 2 (ACE2) combined with Toll-like receptor 4 (TLR4) increases the expression of the NLR family pyrin domain-containing 3 (NLRP3), and exposure to the spike protein increases TLR4 signaling and the inflammasome pathway. This induction is mediated through nuclear factor kappa-B (NF-κB) and p38 mitogen-activated protein kinase (MAPK) due to TLR4 activation. TLR4 is a critical mediator of the neurotoxicity induced by α-synuclein oligomers. α-Synuclein uptake is independent of TLR4. Increased cytosolic DNA levels due to mitotic stress in cancers, cellular senescence or autoimmune disorders may lead to cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) (cGAS–STING) activation and the aggravation of pathological progression [34]. cGAS is an inactive protein in the cell but is activated upon binding to aberrant DNA, which results from viral invasion and senescence. Activated cGAS catalyzes the conversion of cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) to cytosolic DNA. cGAMP binds to STING and triggers STING–tank-binding kinase 1 (TBK1)–interferon regulatory factor 3 (IRF3) signaling. TBK1 kinase phosphorylates IRF3, and phosphorylated IRF3 enters the nucleus. At that point, nuclear factor kappa-B (NF-κB) triggers the expression of interferon-1 (IFN-1) and proinflammatory cytokine genes. The cGAS–STING pathway is a significant nucleic acid recognition pathway. Activated cGAMP is a secondary messenger that activates the STING-dependent IFN-1 response. The sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein (SAMHD1) function at stalled replication forks to prevent interferon (IFN) induction and have a target motif for cyclin-dependent kinase 1 (CDK1), and a CDK-targeted motif that drives threonine 592 (T^{592}) phosphorylation. Phosphorylation of SAMHD1 at residue T^{592} modulates the ability of SAMHD1 to block retroviral infection. CDK1 activity is required for SAMHD1 phosphorylation, which on residue T592 prevents SAMHD1 from blocking retroviral infection. SAMHD1 limits the release of single-stranded DNA and prevents the cGAS–STING pathway inducing the expression of proinflammatory IFN-I. Genetic mutations or unstable four allosteric sites make SAMHD1 tetramerization dangerous and block the cytosolic DNA-sensing pathway

A major key limitation is the rapidly evolving nature of the SARS-CoV-2 virus. As new variants emerge, their specific mechanisms of infection and pathogenesis may differ from those of earlier strains, and further research is needed to understand the dynamics of these changes.

Conclusion

In viral diseases, excessive production, or decreased production of IFN should be an important factor in ultimately worsening pathology. The mechanisms of inflammasome activation, cGAS–STING signaling, and SAMHD1 modulation of innate and adaptive immunity explain the diverse exacerbations of COVID-19.

Method

In 2021, as external activities were difficult during the pandemic era, we analyzed SCI journals about COVID-19 and SARS-CoV-2 through an information search. Key words were connected on the basis of the research results. The inclusion criteria were as follows: (1) ACE2 and TLR, (2) NRP, (3) spike protein, (4) inflammasome activation, (5) cGAS–STING signaling, (6) SAMHD1 tetramerization, (7) immunological memory engram,

Table 3 Approach of COVID-19 papers from 2024-01-04

	The first approach: 2020–2021	The second approach: 2022–2024
1. ACE2 and TLR	Devaux et al. [113] Kumar et al. [114] Chlamydas et al. [115] Ratajczak et al. [82] Lei et al. [116] Kucia et al. [57] Choudhury and Mukherjee [55] Choudhury et al. [117] Patra et al. [118] Zhao et al. [119] Olajide et al. [50] Conte, [63] Zeberg & Pääbo, [58]	Lee, [112] Shirvaliloo, [120] Kronstein-Wiedemann et al. [121] Gonzalez et al. [122] Manik & Singh, [61] Frank et al. [62]
2. NRP	Daly et al. [66] Cantuti-Castelvetri et al. [67] Hoffmann et al. [123] Mollica, Rizzo, and Massari [124] Kyrou et al. [125] Davies et al. [126] Khan et al. [127] Yong [128] Group [129] Li et al. [130] Zeberg and Pääbo [131] Zhang, Wadgaonkar, et al. [77] Clottu et al. [132] Meininger et al. [133] Marini & Gattinoni, [134] Kanwar et al. [38] Ferren et al. [39]	Lee et al. [34] Lucchese et al. [135] Kerner and Quintana-Murci [136] Zhang et al. [137] Spits & Mjösberg, [138] Kawano et al. [139] Dangarembizi & Drummond, [140]
3. Spike protein	Örd, Faustova, and Loog [141] Eisfeld et al. [80] Sergi & Chiu, [142] Shirato and Kizaki [143] Theobald et al. [79] Ren et al. [33] Scully et al. [83] Cai et al. [144] Sahin et al. [145] Tao et al. [146] Idrees & Kumar, [147] Young et al. [148] Chakrabarti et al. [84] Schultz et al. [85] Diaz et al. [81]	Montezano et al. [149] Liu et al. [150] Nyström and Hammarström [151] Prabhakaran et al. [152] Lee, [112] Yao et al. [153] Tyrkalska et al. [154] Szebeni et al. [155]
4. Inflammasome activation	Rodrigues et al. [18] Ferreira et al. [26] Pan et al. [8] Han et al. [95] Rui et al. [96] Lee et al. [52] Lee et al. [53]	Rodrigues and Zamboni [19] Han et al. [89] Deng et al. [97] Beckman et al. [54] Albornoz et al. [51] Wang et al. [21]
5. cGAS–STING signaling	Humphries et al. [99] Yum et al. [90] Cui et al. [91] de Oliveira Mann and Hopfner [32] Paul et al. [37] Fengjuan Li [88]	Domizio et al. [10] Neufeldt et al. [35] Su et al. [93] Liu et al. [12] Chen & Xu, [11]
6. SAMHD1 tetramerization	Bowen et al. [104] Cingöz et al. [48] Yu et al. [105] Khan and Sergi [103] Kwan et al. [111]	Yan, Tang, and Zheng [101] Gupta and Mlcochova [102] Oo et al. [109] Lee et al. [16] Fink et al. [156]

Table 3 (continued)

	The first approach: 2020–2021	The second approach: 2022–2024
7. Immunological memory engram	Troili et al. [157] Baig [158] Dhont et al. [159] Josselyn and Tonegawa [160] Koren et al. [161] Gogolla [162] Zhang, Zhou, et al. [163] Schwabenland et al. [164] Sepehrinezhad, Gorji, and Sahab Negah [165] Lee et al. [166] Yachou et al. [167] Finsterer and Scorza [168] Fu et al. [169]	Ortega-de San Luis et al. [170] Hernandez-Lopez et al. [171] Yang et al. [172] Bar-On et al. [173] Tamari et al. [174]
8. Excess acetylcholine	Mudd et al. [175] Monneret et al. [176] Horkowitz et al. [177]	Erttmann et al. [178] Gabanyi et al. [179] Liu et al. [180] Shahbaz et al. [181] Lee et al. [182] Lee et al. [183] Shim, [184] Axenhus et al. [185] Chen et al. [186]

and (8) excess acetylcholine. Three years after 2021, we checked the experimental results with keywords.

Pathogenesis was analyzed through the first approach (2021) and the second approach (2024). (1) ACE2 and TLR were analyzed in thirteen and six papers; (2) NRP was analyzed in seventeen and seven papers; (3) spike protein was analyzed in fifteen and eight papers; (4) inflammasome activation was analyzed in seven and six papers; (5) cGAS–STING signaling was analyzed in six and five papers; (6) SAMHD1 tetramerization was analyzed in five and seven papers; (7) immunological memory engram was analyzed in thirteen and five papers; and (8) excess acetylcholine was analyzed in three and nine papers. The papers were published on January 4, 2024. Papers published before 2020 were excluded from the presentation to avoid confusion in understanding the pathogenesis of COVID-19 and SARS-CoV-2. Only papers published from 2020 to 2024 are described (Table 3).

Exclusion criteria: If we could not find direct repeated mechanisms with experimental data in SCI journals, those were excluded [187]. The immunological memory engram and excess acetylcholine were analyzed to determine their causal relationships in clinical practice. We temporarily excluded two from the pathogenesis of COVID-19.

Abbreviations

A549 cell	A549 cells are adenocarcinomic human alveolar basal epithelial cells, and constitute a cell line.
ACE	Angiotensin-converting enzyme
AD	Alzheimer's disease
AESI	Adverse events of special interest
AIDS	Acquired immune deficiency syndrome
AGS	Aicardi–Goutières syndrome
AIM2	Absent in melanoma 2
ALI	Air–liquid interface
ALP	Alkaline phosphatase
α-Syn	α-Synuclein
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
APC	Antigen-presenting cells
ARDS	Acute respiratory distress syndrome
ASC	Apoptosis-associated speck-like protein containing a CARD
ATF4	Activated parkin via protein kinase RNA-like endoplasmic reticulum kinase-activating transcription factor 4
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BV-2	A type of microglial cell derived from C57/BL6 mice
CAPS	Cryopyrin-associated periodic syndromes
CARD	Caspase activation and recruitment domain
CCNE2	Essential for the control of the cell cycle at the late G1 and early S phases; belongs to the cyclin family
CCR5	C–C motif chemokine receptor 5
CH	Clonal hematopoiesis, hematopoietic stem and progenitor cells
CDK1	Cyclin-dependent kinase 1
CI	Confidence interval
CK-MB	Creatine kinase-MB fraction
COPD	Chronic obstructive pulmonary disease
COX-1	Cyclooxygenase 1
CRP	C-reactive protein
CRS	Cytokine release syndrome
CtIP	C-terminal binding protein 1 (CtBP1) interacting protein
Cyclin a2	A protein that in humans is encoded by the CCNA2 gene. It is one of the two types of cyclin A: cyclin A1 is expressed during meiosis and embryogenesis while cyclin A2 is expressed in the mitotic division of somatic cells
Cyclin D1	A protein required for progression through the G1 phase of the cell cycle
Cyclin D3	A cofactor of retinoic acid receptors, modulating their activity in the presence of cellular retinoic acid-binding protein II
Cyclin E2	Cyclin E2 is a protein that in humans is encoded by the

	CCNE2 gene
Cyclin-G1	A protein that in humans is encoded by the CCNG1 gene
CXCR-4	C-X-C chemokine receptor type 4
DDS	4,4′-Diaminodiphenyl sulfone (dapsone)
DPP4	Dipeptidyl peptidase-4
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
ER	Endoplasmic reticulum
cGAMP	2′,3′-Cyclic GMP-AMT
cGAS–STING	Cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/ stimulator of interferon genes (STING)
G6PDH	Glucose-6-phosphate dehydrogenase
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1
HSPC	Hematopoietic stem/progenitor cell
ICU	Intensive care unit
IFN	Interferon
IFNAR2	Interferon-alpha and beta receptor subunit 2
IL	Interleukin
IL-1β	Interleukin-1 beta
IMV	Intensive mechanical ventilation
IRF3	Interferon regulatory factor 3
ISG	Interferon-stimulated gene
JNK	Jun N-terminal kinases
LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MDIG	Mineral dust-induced gene
N protein	Nucleocapsid protein
MDA5	Melanoma differentiation-associated gene 5
mRNA	Messenger RNA
mtDNA	Mitochondrial DNA
NACHT	Domain conserved in NAIP, CIITA, HET-E, and TP1
NFL	Neurofilament light chain
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRC4	NLR Family CARD Domain Containing 4
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3, NLR family pyrin domain-containing 3
NRP	Neuropilin
PAMPs	Pathogen-associated molecular patterns
PBMCs	Human peripheral blood mononuclear cells
PEDF	Pigment epithelium-derived factor
PEDFR/iPLA2	PEDF/calcium-independent phospholipase A2
Phosphomimetics	Amino acid substitutions that mimic a phosphorylated protein.
Phospho-p65	Anti-phospho-NFkB p65 (Ser536) monoclonal antibody (T.849.2)
Phospho-IκBα	Phospho-IκBα (Ser32/36) (5A5) mouse mAb #9246
PRMT5	Protein arginine methyltransferase 5
PTGS2	Prostaglandin synthase 2
RIG-I	Retinoic acid-inducible gene I
ROS	Reactive oxygen species
SP	Spike glycoprotein of SARS-CoV-2
S1	SARS-CoV-2 spike protein subunit 1
SAMHD1	Sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein
RCT	Randomized controlled trial
SOD	Superoxide dismutase
TBK1	Tank-binding kinase 1
TGFβ	Transforming growth factor-β
THP-1	A spontaneously immortalized monocyte-like cell line
TNF	Tumor necrosis factor
TLR	Toll-like receptor
TMPRSS2	Transmembrane protease serine subtype 2
TRIF	TLR3-TIR-domain-containing adapter-inducing interferon-β
TTS	Thrombosis with thrombocytopenia syndrome
TREX1	Tthree-prime repair exonuclease 1
TYK2	Tyrosine kinase 2
UCB	Umbilical cord blood
VRD	Viral respiratory disease
VSEL	Very small embryonic-like stem cell

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Declarations

Ethics approval and consent to participate

The National Agency approved this study for the Management of Life-sustaining Treatment, which certified that life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006).

Consent for publication

The authors affirm that the human research participants provided informed consent for the publication of the manuscript results.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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