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Pathology and Anticatalysis Treatment of exacerbated COVID-19

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Treat mechanism: the first line of therapeutics against SARS-CoV-2

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces immune-mediated diseases whose pathophysiology involves the sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein 1 (SAMHD1) tetramerization and cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)– stimulator of interferon genes (STING) signalling pathway, angiotensin-converting enzyme 2 (ACE2), Toll-like receptor 2 (TLR2), and Toll-like receptor 4 (TLR4) pathway with high LPS levels in the blood, inflammasome–spike protein–genetic activation pathway, and innate lymphoid cells with Neuropilin-1 Pathway. They exacerbated COVID-19 type I interferonopathies, and it is necessary to prescribe anticatalytic treatments to alleviate the pathologic course and take the lag time to coordinate innate or adaptive immune cell reactions.

Keywords: SARS-CoV-2; ACE2; TLR4; SAMHD1; **cGAS/STING**; inflammasome; immunologic engram; spike protein; aspirin; dapsone; dexamethasone

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces immune-mediated inflammasome diseases ¹. The coronavirus is an enveloped, nonsegmented, single-stranded, and positive-sense RNA virus, ranging in size from 27 to 32 kb. The large surface glycoprotein gene (up to 4.4 kb) encodes an imposing trimeric, highly glycosylated protein, which is located 20 nm above the virion envelope, giving the virus the appearance (with some imagination) of a crown or coronet ². Corona viruses are divided mainly into four genera, α , β , γ , and δ , based on their genomic structure. α and β coronaviruses infect only mammals. SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are classified as β coronaviruses ³.

Our current perception of COVID-19 immunopathology does not fully elucidate how the innate and adaptive host immune systems appear to miscommunicate to worsen the viral impact and patient prognosis. The bronchoalveolar immune response in coronavirus disease-2019 (COVID-19) has a unique local profile that strongly differs from the immune profile in peripheral blood: T-cell activation in blood, but not in bronchoalveolar lavage fluid (BALF), was higher in fatal COVID-19 cases, and increased levels of inflammatory mediators were more pronounced in BALF than in plasma ⁴. In mild COVID-19, CD8⁺ resident memory and CD4⁺ T-helper-17 cells undergo active expansion, which is presumably antigen-driven ⁵. Severe patients with COVID-19 are associated with increased cytotoxic follicular helper cells and cytotoxic T helper cells and a reduction in regulatory T cells ⁶. Chronic hyperinflammatory monocytes are enriched in critical COVID-19 and contribute to an ATP-purinergic signalling-inflammasome footprint that could enable COVID-19-associated fibrosis and worsen disease severity. Alveolar macrophages are also depleted in critical COVID-19, characterized by anti-inflammatory and antigen-presenting characteristics ⁵.

The pathophysiologic mechanisms driving multiorgan damage include direct viral infection, maladaptive functions of the renin-angiotensin-aldosterone system (RAAS), impact on endothelial cell damage, generation of a thrombotic milieu, dysregulation of the immune response and cytokine release syndrome. Nonetheless, many of the morphological data collected are nonspecific, variable, and possibly associated with other coexisting factors ⁷, such as the mechanisms contributing to endothelial–epithelial barrier breakdown during the invasion process of monocytes and neutrophils. The extravasation of a protein-rich exudate into the alveolar space is consistent with other forms of acute respiratory distress syndrome (ARDS) ⁸. The pathologic ARDS thrombosis is unclear compared to platelets for acute lung injury caused by other respiratory pathogens (bacteria, viruses, plasmodia) ⁹. Angiotensin-converting enzyme 2 (ACE2) is upregulated in lung tissue and serum of COVID-19 ARDS and unrelated ARDS, whereas a loss of type 2 alveolar epithelial (AT2) cells is selectively observed in COVID-19 ARDS. A decrease in AT2 cells may distinguish COVID-19 from unrelated ARDS, whose underlying mechanism may play critical roles in postinjury repair and possibly involves

an increased risk of pulmonary fibrosis ¹⁰. Regardless of the variation in the anti-inflammatory response, pulmonary infection and injury are also associated with systemic inflammation and sepsis ¹¹.

Furthermore, although immune modulation is a promising avenue that is likely to improve treatment outcomes for COVID-19, the most effective targets and intervention strategies remain to be found. Clinical trials of COVID-19 vaccines found high vaccine efficacy, and observational studies evaluated vaccine effectiveness in several countries ^{12 13}. Multiple variants of concern have emerged, such as alpha (B.1.1.7 and Q lineages), beta (B.1.351 and descendent lineages), gamma (P.1 and descendent lineages), epsilon (B.1.427 and B.1.429), Eta (B.1.525), Iota (B.1.526), kappa (B.1.617.1), 1.617.3, Mu (B.1.621, B.1.621.1), zeta (P.2); indeed, more recently Omicron (BA.1), with its submicron subvariants (BA.1.1, BA.2 and BA.3), and other receptor-binding-domain mutants, have also emerged ¹⁴. Some repurposed therapies for COVID-19 have shown benefits, such as the discovery that the selective serotonin reuptake inhibitor, fluvoxamine used in outpatients with COVID-19, was associated with a reduction in hospitalizations ^{15 16}.

Whilst evolving and developing new vaccines for each variant is expensive and time-consuming, there remains an urgent need to identify and block the ARDS pathological process reliably in critical patient scenarios. Recent studies on the investigation of COVID-19 pathology with ARDS and the metabolic action of aspirin, dexamethasone, and 4,4'-diaminodiphenyl sulfone (dapson, DDS) are noteworthy. J.L. et al. reported that dapson played anticatalytic roles in molecular pathologic regulation against exacerbated Alzheimer's disease and viral respiratory diseases (VRD) related to Bronchitis and chronic obstructive pulmonary disease (COPD) ^{17 18}. It will suggest the evidence of the pathologic mechanism of innate lymphoid cells and neuropilin receptors. We will view access to triad medicines as therapeutics and preventive agents for COVID-19 with/without ARDS.

Pathophysiology of COVID-19 Diseases

Suppression of gut microbiota renders mice susceptible to systemic viral infections and the gut microbiota drive systemic antiviral immunity via interferon-1 (IFN-I) priming and microbiota-driven interferon IFN-I priming involves the cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) axis and microbiota mediate systemic IFN-I priming via DNA-containing membrane vesicles in experiment ¹⁹. We explain the pathophysiology of human IFN and its multidimensional roles in regulating senescence, autophagy, apoptosis, antitumor effect, as well as cell metabolism ²⁰.

1. SAMHD1 tetramerization and cGAS–STING signalling pathway

Sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein 1 (SAMHD1) protect cells from viral infections and operate at stalled replication forks to prevent IFN induction, a significant regulator of deoxynucleoside triphosphate (dNTP) concentrations in human cells ²¹. SAMHD1 is a cellular enzyme and depletes intracellular dNTPs. SAMHD1 can restrict retroviruses (human immunodeficiency virus – 1, HIV-1). Mutations in SAMHD1 are linked to the pathogenesis of chronic lymphocytic leukemia and Aicardi-Goutières syndrome (AGS). SAMHD1 contains a target motif for cyclin-dependent kinase 1, whose activity is needed for SAMHD1 phosphorylation. SAMHD1 is phosphorylated on residue threonine 592 (T592) in cycling cells, and phosphorylated SAMHD1 on T592 cannot block retroviral infection. However, this modification does not affect the ability of SAMHD1 to decrease cellular dNTP levels. Phosphorylation modulates SAMHD1 to block retroviral infection without affecting its ability to decrease cellular dNTP levels ²². A phosphomimetic mutation surrounding T592 triggered electrostatic repulsion from a distinct negatively charged environment. This resulted in a significant decrease in active SAMHD1 tetramers, and hence, the dNTPase activity was substantially decreased. SAMHD1 phosphorylation at residue T592 may modulate its cellular and antiviral functions ²³.

The downregulation of SAMHD1 by small interfering RNA (siRNA) expands all four dNTP pools, which consist of deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine triphosphate (dCTP) and deoxythymidine triphosphate (dTTP) nucleotides. SAMHD1 releases deoxyguanosine from dGTP. And SAMDH1 can be phosphorylated inside mitochondria by deoxyguanosine kinase (dGK) or degraded in the cytosol by purine nucleoside phosphorylase. SAMHD1 contributes to the pathological phenotype of dGK deficiency in regulating the dGTP pool during quiescence, and it engaged dGK-mutated skin fibroblasts derived from three unrelated patients. SAMHD1 quiescent mutant fibroblasts showed a mitochondrial (mt) dNTP pool imbalance and mtDNA depletion.

Mitochondrial antiviral signalling proteins are linked with SAMHD1. Genetic mutations of dGK can cause mtDNA depletion in noncycling cells and hepatocerebral mtDNA depletion syndrome in humans ²⁴.

Inactive apo-SAMHD1 interconverts between monomers and dimers, and the binding of dGTP to four allosteric sites promotes tetramerization and induces a conformational change in the substrate-binding pocket to yield the catalytically active tetramer ²⁵. The binding sites are plastic, and the allosteric binding sites can adjust oligonucleotides in place of the allosteric activators GTP and dNTP. The binding of G-nucleotide-containing oligonucleotides in the presence of GTP and dNTPs promotes the formation of a specific tetramer with mixed occupancy of the allosteric sites responsible for the antiretroviral activity of SAMHD1 ²⁶. SARS-CoV-2 infection strongly regulates cyclin-dependent kinase (CDK) signaling pathways to provide favorable circumstances for viral replication, particularly by lowering CDK1/2 activity, and it results cell cycle S and G2 like phase arrest. It is similar to that generated by other RNA viruses ²⁷. Hepatitis B virus (HBV) recruits cyclin E2 to bind CDK2 and further phosphorylated SAMHD1 to abrogate its restriction of HBV replication. CDK1, CDK2, and CDK6 inactivate antiviral protein SAMHD1 phosphorylation, and CDK11 collaborates with Cyclin L2 to induce SAMHD1 degradation to facilitate HIV-1 replication ^{28 29}. SARS-CoV-2 enhances the phosphorylation of CDK2 at locations T14 and Y15, inhibiting premature cellular entrance into mitosis ²⁹. SARS-CoV-2 might use CDK2 to phosphorylate SAMHD1 like HBV for its adequate replication.

(Figure 1)

The SAMHD1 tetramer structure could provide a mechanistic understanding of its rapid function in SARS-CoV-2. SAMHD1 negatively regulates the IFN-1 signaling pathway: the elevated innate immune response and IFN activation upon genetic loss of SAMHD1 effectively suppresses SARS-CoV-2 replication ³⁰. The spontaneous IFN response requires cGAS/ STING cytosolic DNA-sensing pathway in SAMHD1-deficient cells and mice. SAMHD1 mutations cause autoinflammatory AGS, which is characterized by chronic type I IFN secretion in the absence of infection with exogenous viruses ³¹ and typified by early-onset brain disease ³². IFN gamma (γ) is a dimerized soluble cytokine and its signaling is upregulated in COVID-19 human neurovascular unit ³³. SARS-CoV-2 evokes a response that requires the strong induction of a subclass of cytokines, including type I and, obviously, type III IFN and a few chemokines, such as those produced in response to influenza A virus and, in particular, respiratory syncytial virus ^{21,34}. SAMHD1 limits the virus-induced production of IFNs and the induction of costimulatory markers during lentivirus infection in myeloid cells. This programmed myeloid cell activation required reverse transcription, cGAS and STING, and signalling through the interferon receptor. Furthermore, SAMHD1 reduced the induction of virus-specific cytotoxic T cells in vivo.

SAMHD1 limits the control of virus infection through innate and adaptive immunity at the level of the infected cell ³⁵.

cGAS catalyzes the production of cGAMP (cyclic guanosine monophosphate-adenosine monophosphate) upon sensing cytosolic DNA, which activates STING–TBK1 (tank-binding kinase 1)–IRF3 (interferon regulatory factor 3) signaling. cGAS is present in the nucleus, and nuclear cGAS is sequestered at chromatin in an inactive state. Nuclear cGAS recruits Prmt5 (protein arginine methyltransferase 5, facilitating IRF3 access) upon viral infection. Nuclear-localized cGAS, in innate immunity, interacts with Prmt5 to catalyze the symmetric dimethylation of histone H3 arginine 2 at IRF3-responsive genes (*Ifnb* and *Ifna4*) ³⁶. Active cGAS produces cyclic GMP-AMP (cGAMP), which binds to STING. STING relocates to the perinuclear Golgi and forms a clustered platform where the TBK1 kinase phosphorylates the transcription factor IRF3. Phosphorylated IRF3 enters the nucleus and, along with the nuclear factor kappa-light-chain-enhancer of activated B cells, triggers the expression of type I IFN and proinflammatory cytokine genes ³⁷. The cGAS–STING has been identified as a significant nucleic acid recognition gene. cGAS typically resides as an inactive protein in the cell and is activated upon binding to aberrant DNA. Activated cGAS then synthesizes 2',3'-cGAMP, which acts as a secondary messenger that activates STING. cGAS–STING responds to foreign DNA from viruses and bacteria and to mitochondrial and genomic self-DNA, which enters the cytosol from senescent or dying cells ³⁸. SARS-CoV-2 infection could induce syncytia formation within cells expressing ACE2 and the SARS-CoV-2 spike protein, producing micronuclei at an average rate of approximately four per syncytium (> 93%). These micronuclei were expressed with a high activation level for the DNA damage response and cGAS–STING signalling. These signalling pathways were associated with cellular catastrophe and aberrant immune activation at the cellular and molecular levels. Activated STING triggers membrane permeabilization and thus lysosomal cell death ³⁹.

2. ACE2, TLR2, and TLR4 pathways with high LPS levels in the blood

An interaction between SARS-CoV-2 spike protein (S) and lipopolysaccharide (LPS) leads to aggravated inflammation *in vitro* and *in vivo* ⁴⁰. This links high LPS levels in the blood and metabolic syndrome. Metabolic syndrome predisposes patients to severe COVID-19. ARDS is a general systemic inflammatory reaction common to pneumonia, severe infection, sepsis, burns, and severe trauma. During ARDS, activation of toll-like receptors (TLRs), such as Toll-like receptor 4 (TLR4), via LPS stimulation induces an initial systemic proinflammatory phase characterized by a massive release of cytokines, acute phase proteins, and reactive oxygen species (ROS) ⁴⁰.

Toll-like receptor 2 (TLR 2) and TLR4 (CD284) are expressed intracellularly in dendritic, epithelial, and endothelial cells ⁴¹. ACE2 expression in the lungs is shallow compared to that in other organs, such as the heart, kidneys, and small intestines ⁴². The SARS-CoV-2 spike (S) protein subunit 1 of the spike glycoprotein (S1) has been proposed to have the most substantial protein-protein interaction with TLR4 ⁴³. The bronchial mucosa at the air-liquid interface was developed using primary bronchial epithelial cells, and the alveolar lung mucosa at the air-liquid interface was representative of type II pneumocytes (alveolar type 2 cell, AT2). Exposure to S1 protein induced the surface expression of ACE2, TLR 2, and TLR4 in both bronchial and alveolar lung mucosa models at the air-liquid interface. It revealed enrichment of canonical pathways such as IFN signaling to influenza, coronavirus, and anti-viral response in the bronchial mucosa. Interleukin-4 (IL-4) and interleukin-12 (IL-12) were significantly increased ($p < 0.05$), but interleukin-6 (IL-6) was decreased in the bronchial mucosa. In the alveolar mucosa, enriched p53, a proliferation-inducing ligand (APRIL) tight junction, integrin kinase, and interleukin-1 (IL-1) signalling were identified. These are associated with pulmonary fibrosis.

Proinflammatory cytokines (IFN γ , IL1 β , IL2, IL4, IL-6, interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-13 (IL-13), and tumor necrosis factor-alpha (TNF-a)) were detected to be significantly increased in the alveolar mucosa ($p < 0.05$), whereas IL-12 was decreased. Altered levels of these cytokines are also associated with fibrotic lung response ⁴⁴. S protein activates the nuclear factor- κ B (NF- κ B) pathway, and S protein-mediated activation of the NF- κ B pathway is TLR2 dependent. TLR2 senses the SARS-CoV-2 envelope protein, but TLR2 requires heterodimerization with TLR1 or TLR6 to sense the S protein ⁴⁵. TLRs are critical sensors of innate immunity that recognize pathogen-associated molecular patterns and activate downstream signaling for proinflammatory cytokine and chemokine production, but dysregulated TLR responses may enhance immune-mediated pathology ⁴⁶. S1 contains the ACE2 receptor binding domain. Thus, the inhomogeneous phenotypes of COVID-19-associated ARDS illustrate important clinical descriptions and may have diverse therapeutic implications. Many ACE2 and TLR4 are expressed on hematopoietic stem and progenitor cells (HSPCs), which are highly susceptible to the spike protein. ACE2 and TLR4 belong to the

pattern recognition receptor (PRR) family on the cell surface and are responsible for the production of inflammatory cytokine and the activation of innate immune responses. S protein infects erythroid progenitors and dysregulates⁴⁷.

TLR4 plays an essential role in mediating the neurotoxicity induced by α -synuclein oligomers. Misfolded α -synuclein (α -Syn) induces inflammatory responses, and extracellular α -Syn can activate proinflammatory TLR4 pathways in astrocytes; however, α -Syn uptake is independent of TLR4⁴⁸. The interaction between TLR4 and S can trigger an intracellular TLR4 signaling cascade. NF- κ B's transcriptional activation of specific genes induces the release of proinflammatory cytokines, which can cause neuronal damage and the pathological modification of α -Syn⁴⁹. Interference with the S interaction with cell-surface-expressed ACE2 and TLR4 decreased the activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome's downstream mediator caspase-1, and this suppression was even more noticeable when the interaction of S with both receptors was blocked. Exposure to S upregulates the expression of proteins involved in the positive stimulation of the TLR4 signalling pathway⁴⁷. SARS-CoV-2 also activates TLR4, leading to the activation of NF- κ B and, ultimately, the production of immature IL-1 β (pro-IL-1 β).

NF- κ B activation is central to the acute respiratory RNA virus-induced cytokine storm. Moreover, SARS-CoV-2-induced TLR4-mediated NF- κ B activation has been reported⁵⁰. S protein induces neuroinflammation in BV-2 microglia (a type of microglial cell derived from C57/BL6 mice). Immunofluorescence microscopy revealed an increase in TLR4 expression in BV-2 microglia stimulated with S1. The induction of neuroinflammation in microglia is mediated through the activation of NF- κ B and p38 mitogen-activated protein kinase (MAPK), possibly due to TLR4 activation⁵¹. Peripheral infections, including influenza A⁵², *E. coli*⁵³, and HIV⁵⁴, have been associated with memory impairments. Due to synaptic plasticity, increased proinflammatory cytokine expression affects immune-to-brain communication and sickness behavior. Mature interleukin-1 β (IL-1 β) exerts multiple effects on synaptic-plasticity-related processes. For example, it suppresses brain-derived neurotrophic factor (BDNF) production and reduces α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. AMPA receptors facilitate fast synaptic transmission in the central nervous system (CNS) and are composed of glutamate A1-4 as ionotropic glutamate receptor subunits. IL-1 β inhibits long-term potentiation when it is released into the extracellular fluid. IL-1 β in neurons is critical for developing adaptive sickness behaviors⁵⁵. The final sequence of NF- κ B activation is shared with a range of cytokine-receptor and TLR-mediated signaling cascades.

3. Inflammasome–spike protein–genetic activation pathway

SARS-CoV-2 engages inflammasomes and pyroptosis is associated with caspase-1 activation, IL-1 β production, gasdermin D cleavage, and enhanced proinflammatory cytokine levels in human primary monocytes⁵⁶. Inflammasomes are named after different sensing proteins, and there are four main types: NLRP1, NLRP3, NLRC4, and AIM2. The NLRP3 inflammasome has crucial functions in RNA virus infection. Inflammasome is composed of NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1⁵⁷. ASC is a 22 kDa protein that functions as the central adaptor for inflammasome assembly and forms insoluble specks in monocytes undergoing pyroptosis, and only insoluble form of ASC promoted caspase-1 autocatalysis in canonical inflammasomes⁵⁸.

The NLRP3 inflammasome has ① a sensor protein, ② an adaptor protein, ASC; and ③ an effector protein, caspase-1. The NLRP3 protein has the pyrin (PYD), nucleotide-binding, and leucine-rich repeat domains. First, NLRP3 PYD interacts with ASC PYD; second, it promotes ASC oligomer formation; third, insoluble ASD provides a platform for caspase-1 activation during the activation of the NLRP3 inflammasome^{57 58}.

Active caspase-1 is formed by autocatalytic cleavage, which then catalyzes the proteolytic processing of pro-interleukin (IL)-1 β into mature IL-1 β . NLRP3 deubiquitination and self-aggregation first occur during the activation of the NLRP3 inflammasome, followed by ASC recruitment and oligomerization, and then procaspase-1 is cleaved into active caspase-1, which can cleave pro-IL-1 β and pro-IL-18 to produce mature IL-1 β and IL-18⁵⁷.

Excessive IL-1 β stimulates systemic inflammatory responses by activating various signaling pathways, such as the NF- κ B and Jun N-terminal kinases (JNK). As a result, cytokines are released at large amount, and IL-6, tumor necrosis factor (TNF), IFN- α , IFN- β , and transforming growth factor- β can lead to a “cytokine storm” in acute inflammatory diseases. SARS-CoV-2 encodes several accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8, and ORF10). Further studies have revealed that the envelope protein and ORF3a of SARS-CoV activate the NLRP3 inflammasome by changing the K⁺ ion permeability of the plasma membrane and the production of mitochondrial reactive oxygen species. However, the specific molecular mechanism by which SARS-CoV-2 activates NLRP3 inflammasomes is unclear⁵⁷.

Longitudinal analyses have revealed robust S-driven inflammasome activation in macrophages isolated from convalescent COVID-19 patients, which correlates with distinct epigenetic and gene expression signatures. S-driven IL-1 β secretion from patient-derived macrophages requires nonspecific monocyte preactivation *in vivo* to trigger NLRP3 inflammasome signalling. SARS-CoV-2 infection causes profound and long-lived reprogramming of macrophages, resulting in augmented immunogenicity of SARS-CoV-2, an effective vaccine and immune signalling⁵⁹. SARS-CoV-2 nucleocapsid (N) can directly

interact with NLRP3, leading to the production of many inflammatory factors and lung injury in mice. Inhibiting the NLRP3 inflammasome can reduce cytokine storms and lung injury ⁵⁷.

Spike protein–induced pathway

An adenovirus vector or lipid nanoparticle (LNP)-encapsulated mRNA encoding the full-length S protein (or various modifications) can induce a robust adaptive immune response by different types of activated B and T lymphocytes. Although the protein expression may be limited primarily to the APCs near the injection site and draining lymph nodes, some degree of expression may occur in distant organs because of systemic spread ⁶⁰. A nucleoside-modified mRNA formulated in LNPs encodes S protein, and S drives inflammasome activation in macrophages isolated from convalescent COVID-19 patients, which correlates with distinct epigenetic and gene expression signatures ⁵⁹.

Molecular docking studies further suggest that the interaction of S with prion protein is more robust than that with amyloid-beta, tau or α -synuclein ⁶¹. The hyperinflammatory state in COVID-19 features high proinflammatory cytokines, and it might trigger CNS neuroinflammation by activating astrocytes and microglia, which could facilitate prion-like pathology ⁶². In addition, similar to other prion proteins, the S-protein also contains several prionogenic domains. Thus, a direct toxic action of S, triggering a neurodegenerative condition mimicking a prion-disease-like pathology, is also possible ⁶³ ⁶⁴. A previously healthy woman in her 60 s, after the second dose of the ChAdOx1 nCoV-19 vaccine, showed diffusion restriction and patchy diffusion restriction in the left posterior parietal and occipital gyri and showed an increase in the degree of FLAIR hyperintensity after 16 days, which was a cortical ribboning pattern of hyperintensity in diffusion MRI. An electroencephalogram (EEG) revealed bilateral biphasic and sharp triphasic wave periodic discharges of approximately 1 Hz, slowing background activity ⁶³. Cross-reactive antibodies might be the origin of many of the reported complications following COVID-19 vaccines, such as Guillain–Barre syndrome, immune thrombotic thrombocytopenia and stroke events, and exacerbations of demyelinating diseases ⁶⁵. S leads to micronuclei production, and these micronuclei manifested with strong activation of the DNA damage response and cGAS–STING signalling ³⁹. Type I IFN antiviral gene expression transiently declined during radiotherapy for cancer patients but promptly recovered after radiotherapy. SAMHD1, which is involved in suppressing viral replication, and the suppression of viral-response genes occurred more frequently in severe ventilation-associated COVID-19 cases than in nonventilated cases ⁶⁶. The degradation of SAMHD1 in human primary-activated/dividing CD4⁺ T cells, the elevation of cellular dNTP levels ⁶⁷, and the loss of dNTPase activity contribute to the elevated dNTP levels commonly found in cancer cells ⁶⁷. S with micronuclei can damage DNA and increase SAMHD1–cGAS–STING signalling ³⁹. Two distinct myocarditis and pericarditis have been observed after COVID-19 vaccination ⁶⁸.

4. Innate lymphoid cells with Neuropilin-1 Pathway

Neuropilin-1 (NRP1) is expressed in all vertebrates and constitutes coreceptors for various molecules, such as a pleiotropic single transmembrane coreceptor for class-3 semaphorins and vascular endothelial growth factors⁶⁹. NRPs are involved in cell proliferation, angiogenesis, vascular permeability, immune function, neuronal development, and axon control. In addition, NRP1 contributes to the tissue/organ tropism of SARS-CoV-2⁶⁹.

The expression of NRP1 has been observed in the respiratory tract, blood vessels, and neurons. NRP1 plays essential roles in axonal guidance in neurons, in the growth of new blood vessels, and regulatory T cells' immune response. NRP1 showed the multifaceted roles in memory CD8 T cell differentiation, dependent upon the stage of the T cell response and characteristics of the infectious agent. Molecule NRP1 plays an important and complex role in the secondary CD8 T cell response to control virus infections and tumors⁷⁰. We can divide Innate lymphoid cells (ILCs) into three groups based on distinct cytokine secretion profiles and the transcription factors they depend on. Group 3 ILCs (ILC3s), dependent on the transcription factor retinoic acid-related orphan receptor- γ (ROR γ t), are present in lymphoid tissues. ILC3s with NRP1 produce higher cytokines than ILC3s without NRP1⁷¹. NRP1⁺ ILC3 cells are present at high frequencies in fetal tissues and postnatal secondary lymphoid organs during embryogenesis but not in blood or skin. NRP1⁺ ILC3 are present in ectopic lymphoid aggregates in patients with chronic lung disease. NRP1⁺ ILC3 play a potential role in inflammation and vascularization⁷².

(Figure 2)

It is well-established that the entry of SARS-CoV-2 into host cells is facilitated by NRP1 and similar neuropilin-1 (NRP2). They bind peptides formed upon furin cleavage. NRP1 is a highly conserved transmembrane receptor that lacks a cytosolic protein kinase domain and significantly potentiates SARS-CoV-2 infectivity^{73,74}. NRP1 is expressed in olfactory-related regions such as the olfactory tubercles and paraolfactory gyri of the CNS⁷⁵. The mineral dust-induced gene (MDIG), arsenic (As³⁺), induces the expression of genes that facilitate SARS-CoV-2 infection and increases metabolites involved in protein glycosylation. MDIG is an environmentally induced lung cancer oncogene and is an essential regulator of NRP1 and NRP2. MDIG is mainly responsible for the expression of inflammatory cytokines, the critical component of the inflammasome, and most of the genes in glycan metabolism for hyaluronan generation and glycosylation. It also antagonizes the repressive trimethylation of histone proteins and regulates cathepsins, glycan metabolism and inflammation⁷⁶. MDIG is elevated in pulmonary fibrosis and is a critical factor in developing lung fibrosis associated with COVID-19, chronic bronchitis, pneumonia, and cancer⁷⁶.

Smoking affects ACE2 expression ⁷⁷ and induces MDIG, which alters the transcription of several essential proteins implicated in the development of COVID-19 ⁷⁸. This type of epigenetic regulation of gene expression links genotype and phenotype by altering the function of the gene locus without changing the underlying DNA sequence. It relies on posttranslational chemical changes at the chromatin, RNA, and DNA levels, including primary methylation and acetylation, phosphorylation, and ubiquitination sumoylation ⁷⁹.

NRP1 and NRP2 may be critically required for efficient viral entry into host cells in the lung. MDIG entry into the two additional cell lines (MDA-MB-231 and A549) depends on the expression of NRP1 and NRP2. MDIG plays a critical role in SARS-CoV-2 infection and the severity of COVID-19 among patients who have a history of environmental exposure to toxins. These effects are attributable to pulmonary fibrosis among some COVID-19 survivors. The MDIG-dependent expression of NRP1 or NRP2 enhances SARS-CoV-2 infection of cells with lower ACE2 expression ⁷⁶. NRP1, which is induced postnatally and sustained by lung-derived transforming growth factor beta-1 (TGFβ1), is a tissue-specific marker of lung Group 2 innate lymphoid cells (ILC2s). TGFβ1–NRP1 signaling enhances ILC2 function and type 2 immunity, which identifies NRP1 as a tissue-specific regulator of lung-resident ILC2s and features an NRP1 regulator as a potential therapeutics for pulmonary fibrosis ⁸⁰. An inhibitor of NRPs will facilitate the development of effective management strategies that improve the outcomes of COVID-19 patients. This study will suggest the therapeutics.

Immunological engram-induced pathway

SARS-CoV-2 may move from the periphery into the CNS through olfactory neurons or the vagus nerve from the lungs or gut ^{81 82}. SARS-CoV-2 may disrupt the blood–endothelial barrier by damaging the choroid plexus epithelium due to cytokine storms and systemic inflammation through neuronal cell-surface receptors ^{83 33}.

(Figure 3)

The different cell types, including dopaminergic neurons, cortical neurons, brain microvascular endothelial cells, and choroidal epithelial cells, are susceptible to SARS-CoV-2, but there are differences in permissiveness. SARS-CoV-2 is neurovirulent and not restricted to patients with mild or severe diseases and can develop neurological complications. We found activated microglia in the olfactory bulb, midbrain (specifically, in the substantia nigra), hindbrain, dorsal motor nucleus of vagus nerve, and pre-Bötzinger complex on the medulla ⁸⁴. Clinically, COVID-19 ARDS can present with relatively preserved aeration on chest computed tomography (CT) imaging despite severe respiratory hypoxemia. However, this early, high-compliance phenotype evolves into a low-compliance phenotype with poor aeration in some

patients. We described the first clinical presentation of the L-type as low elastance (high compliance), low lung weight, low lung recruitment ability, low deranged ventilation-perfusion ratio (VA/Q), preserved aeration and the second H-type as a severe ARDS-like picture of hypoxemia, bilateral infiltrates, and increased lung weight. On CT scans, these patients have higher lung weight, high elastance (low compliance), and a high response to PEEP, meaning that nonaerated lung tissue is very high ⁸⁵. COVID-19 patients with type L respiratory failure exhibit poor oxygenation but have high minute ventilation. Infiltrates seen on CT scanning have a ground glass appearance that implies interstitial edema rather than alveolar edema ⁸⁶. These patients are not overtly dyspneic despite an oxygen saturation below 90%. COVID-19 causes unique lung injury of the type L or H type and needs different ventilatory approaches to the underlying physiology. COVID-19 may stabilize with the engram pathway at this point without further deterioration. This could explain the L-type rapid respiratory distress and sudden death. Neuroinflammation with microgliosis and T-cell infiltration in COVID-19 brains was significantly greater than in patients who did not have COVID-19 ⁸⁷. We could explain the respiratory failure by brainstem involvement with pre-Bötzinger complex involvement and sudden high death rate of COVID-19 ARDS patients ^{88 89}.

In many cases, there is no direct virus attack on vulnerable structures. Instead, the neurological disease manifestations may be due to the immune reaction against the virus, and preexisting neurological disease may become clinically evident or worsen with COVID-19, which explains why various nervous system manifestations react favourably to immune suppression or immune modulation ^{86 90}. The insular cortex stores immune-related pieces of information. The chemogenetic reactivation of these neuronal bands was sufficient to broadly retrieve the inflammatory state of these neurons that was depicted in the insular cortex ⁹¹. These immunological memory engrams, as memory traces, can restore the initial disease state ⁹². The brain remembers immune challenges, regulates peripheral immunity, and can exacerbate the process of immune reactions ⁹³. Microglia and astrocytes play specific and dynamic roles during immune activation. This immune-to-brain communication occurs when glia, microglia, and astrocytes interpret and propagate inflammatory signals in the brain and influence physiological and behavioral-change responses. Astrocytes can develop an immunosenescent profile with age. Astrocyte immunosenescence and deficits in IL-10 signalling in the aged brain disrupt the regulation of microglia following innate immune activation ^{94 95}. Activating the peripheral immune system with a coordinated brain response should elicit and influence physiological and behavioural responses in the immune-to-brain communication pathway.

The genome-wide DNA methylation profiles of severe COVID-19 cases revealed increased methylation of IFN-related genes, while inflammatory genes were hypomethylated ⁹⁶. An interferon stimulating gene (ISG) expression signature is a hallmark of interferonopathies and other autoimmune diseases. Combined inhibition of histone deacetylases (HDAC) and bromodomain-containing protein 4 (BRD4) resolved the aberrant ISG expression detected in cells derived from patients with two inherited interferonopathies ⁹⁷.

(Table 1)

Therapeutics for type 1 interferonopathies of COVID-19

1. Aspirin Treatment Metabolism

SARS-CoV-2 infection induces COX-2 expression

Nonsteroidal anti-inflammatory drugs (NSAIDs) effectively block the production of prostaglandins (PGs) via the inhibition of cyclooxygenase enzymes ⁹⁸. PGs and cytokines synergistically activate NF- κ B to induce the expression of inflammation-related genes, one being cyclooxygenase 2 (COX-2), which is often highly expressed in tissues in chronic disorders, resulting in PG-mediated positive-feedback loops. These signalling loops enhance the expression of various NF- κ B-induced genes, including chemokines, in macrophages and neutrophils, enabling the sustained infiltration of these cells and further amplifying chronic inflammation. Moreover, PGs are involved in fibrosis and angiogenesis ⁹⁹. SARS-CoV-2 infection induces prostaglandin synthase 2 (PTGS2)/COX2 expression in human cells and mice. SARS-CoV-2 infection induces COX-2 expression, which indicates that NSAIDs could modulate COVID-19 severity by dampening neutralizing antibodies and inflammatory cytokines ¹⁰⁰. Aspirin treats inflammation by inhibiting COX, and the aspirin-mediated inhibition of cGAS activation is not related to its effect on COX; however, another specific COX inhibitor, diclofenac, did not affect cGAS activation ¹⁰¹.

However, PGs can also be immunosuppressive in specific contexts, such that NSAIDs may counterintuitively promote immune responses. For instance, age-dependent increases in prostaglandin D₂ (PGD₂) correlate with progressive impairment in respiratory dendritic cell migration, and they are associated with virus-specific defects in T cells ¹⁰². Prostaglandin E₂ (PGE₂) inhibits macrophage recruitment to the lungs during influenza A virus infection and type I IFN production and apoptosis in macrophages infected with influenza A virus ¹⁰³. PGD₂ and PGE₂ have been shown to impair both innate and adaptive immunity to influenza A virus, with PGD₂ having a similar impact on SARS-CoV. After viral infection, inflammasome activation and the expression of a downstream proinflammatory cytokine, IL-1 β , were increased in mice deficient in PGD₂ signalling. Increased mortality by blocking prostaglandin signalling was reversed by IL-1 β receptor blockade. PGD₂ signaling modulates excessive inflammation and tissue damage in the virus-infected brain. PGD₂ signaling prevents excessive inflammasome activation during murine coronavirus-induced encephalitis ¹⁰⁴. Therefore, reducing PGD₂ and PGE₂ levels with NSAID treatment could improve the induction of antiviral immunity. Conversely, low expression of prostaglandin I₂ (PGI₂) could have detrimental effects on the resolution of infection because PGI₂ is antiviral in respiratory syncytial virus infection ¹⁰⁵. Furthermore, the chronic use of NSAIDs that inhibit COX-2 activity or expression blunts the ability of B cells to produce antiviral antibodies, thereby making vaccines less effective and possibly increasing susceptibility to viral infection ¹⁰⁶.

Finally, NSAIDs may inhibit the production of antibodies to SARS-CoV-2, which has been observed for other viruses, but its effect on COVID-19 severity has been unclear because antibodies can be protective or pathogenic ¹⁰⁷.

The ability of NSAIDs to modulate the immune response to SARS-CoV-2 infection has important implications for COVID-19 pathogenesis; however, NSAID treatment reduced both the antibody and proinflammatory cytokine responses after SARS-CoV-2 infection ¹⁰⁰. Altogether, given PGs' complex and sometimes conflicting roles, the overall effect of NSAIDs on the immune response to SARS-CoV-2 dampens COVID-19 severity.

Aspirin inhibited Cgas and does not affect STING directly.

Aspirin inhibited cGAS-mediated interferon production and alleviated DNA-induced autoimmunity in AGS mouse models and patient cells ¹⁰¹. cGAS acetylation on Lys384, Lys394, or Lys414 contributes to keeping cGAS inactive. Aspirin can quickly acetylate cGAS and powerfully inhibit cGAS-mediated immune responses ^{108 101}. Aspirin can effectively suppress self-DNA-induced autoimmunity in AGS patient cells and an AGS mouse model. Acetylation contributes to cGAS activity control and provides a potential therapy for treating DNA-mediated autoimmune diseases ¹⁰¹. cGAS activates downstream IRF3 and NF-κB signalling via STING ¹⁰⁹, and both are involved in IFN production ¹¹⁰. NF-κB can adjust the expression of some ISGs ¹¹¹. Aspirin may deter the activation of both IRF3 and NF-κB by targeting cGAS as a definite cGAS inhibitor

(Figure 4).

Aspirin strongly inhibited cGAS-mediated TBK1–IRF3 signaling. However, aspirin does not affect STING activator cGAMP- or cyclic di-guanosine monophosphate (c-di-GMP)-induced downstream TBK1–IRF3 signalling and does not inhibit STING-associated vasculopathy with onset in infancy (SAVI)-associated STING mutant-mediated IRF3 activation. Aspirin inhibits the DNA–cGAS–STING–TBK1–IRF3 axis through inhibition of cGAS ¹⁰¹. With an acetyl-lysine-incorporating protein synthesis system, Chen et al. created recombinant acetylated cGAS proteins and showed that acetylation of these residues strongly inhibits the activity of cGAS and that these acetylation sites participate in the DNA binding of cGAS. The DNA-binding activity of cGAS is slightly reduced by acetylation on each of the individual sites for recombinant acetylated cGAS proteins, consistent with a previous study showing that mutations on some of these residues have only a limited influence on the DNA binding of cGAS. There are six lysine (K) acetylation sites for cGAS: K7, K50, K384, K392, K394, and K414. When K384, K394, or K414 is acetylated, other regions of cGAS, such as the N-terminal region, could still contribute to DNA binding. Several regions of the cGAS

protein are essential for cGAS–DNA binding, and the binding of DNA to cGAS leads to the deacetylation of cGAS, promoting cGAS activation. K384 and K414 of cGAS are critical residues for cGAS regulation by multiple posttranslational modifications (PTMs). cGAS undergoes K48-linked ubiquitination at K414, leading to the p62-dependent selective autophagic degradation of cGAS in resting cells, and upon DNA-virus infection, this inhibitory ubiquitination is removed, promoting cGAS activation ¹¹⁰. The histone deacetylase (HDAC)-mediated removal of K384 acetylation may allow K27-linked ubiquitination on K384 to further promote cGAS activation ¹⁰¹. Acetylation on K414 may compete with ubiquitination to maintain an adequate level of cGAS protein in resting cells, and K27-linked ubiquitination on K384 of cGAS has been shown to potentiate cGAS activity in response to DNA-virus infection ¹¹².

Aspirin treatment decreased mortality.

Patients progress rapidly to acute respiratory distress syndrome (ARDS), and in the underlying form, septic shock, irreversible metabolic acidosis, blood coagulation dysfunction, or hemostatic and thrombotic anomalies are the leading causes of death due to COVID-19. Platelets play a crucial role in developing severe disease cases and are the enucleated cells responsible for thrombus formation and the hyperreactivity induced by proinflammatory microenvironments in the more aggressive course of COVID-19 ¹¹³. Disseminated Intravascular Coagulation (DIC) may upregulate the coagulation pathways by activating procoagulant factors such as tissue factors, leading to arterial and venous thrombotic disease ¹¹⁴. This high cytokine level is critical in the morbidity and mortality of COVID-19 patients, and cytokine storm syndrome contributes to the upregulation of metabolic coagulation pathways, resulting in damage to the endothelium and the cardiovascular system ¹¹⁵. The antithrombotic properties of aspirin make it a plausible drug for preventing thrombotic disease because aspirin inhibits platelets and inflammatory cytokines that lead to pathologic platelet aggregation. As a result, aspirin can prevent clot formation and reduce the risk of deep vein thrombosis recurrence by 34%, without significantly increasing the risk of bleeding, but not the thrombolysis of an existing clot ¹¹⁶. Aspirin can modulate multiple pathogenic mechanisms implicated in developing multiple organ dysfunction in sepsis and ARDS ¹¹⁷. A water-soluble salt of acetylsalicylic acid and two amino acids, glycine and lysine (licensed as aspirin iv.®, Tamiflu®), was shown to inhibit NF-κB activation and alleviate influenza symptoms in hospitalized patients ¹¹⁸.

Early in the COVID-19 pandemic, there was concern that NSAIDs could be related to adverse cardiovascular and pulmonary outcomes, and some suggested potential harm with NSAID prescription for COVID-19 patients ¹¹⁹. There are many aspirin contraindications to consider, such as in the setting of DIC and other bleeding disorders. Aspirin use can result in uncontrolled hemorrhage and poses a risk of Reye's syndrome in children. However, we found

no evidence of a harmful effect of NSAIDs on COVID-19-related deaths. The risks of COVID-19 do not need to influence decisions about the therapeutic use of NSAIDs ¹²⁰. In this cohort of COVID-19 patients, ibuprofen use was not associated with worse clinical outcomes ¹²¹. NSAID and angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) use prior to admission is not associated with renal failure or increased mortality ¹²². The acute or chronic use of ibuprofen and other NSAIDs was not associated with worse COVID-19 disease outcomes ¹²³. NSAID use might confer a modest benefit concerning survival ¹²⁴. NSAIDs were not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in Danish individuals who tested positive for SARS-CoV-2 ¹²⁵. In a study, veteran patients were matched via propensity scores, which resolved the differences in age, gender, and Care Assessment Needs (CAN) score, and the odds of mortality were then compared; the study involved 35,370 subjects from March 2, 2020, to September 13, 2020, for the 14-day mortality cohort and 32,836 subjects from March 2, 2020, to August 28, 2020, for the 30-day mortality cohort. Among the COVID-19-positive veterans, a preexisting aspirin prescription was associated with a statistically and clinically significant decrease in overall mortality at 14 days (OR, 0.38; 95% CI, 0.32–0.46) and 30 days (OR, 0.38; 95% CI, 0.33–0.45). Prediagnosis aspirin prescription was strongly associated with decreased mortality rates for veterans diagnosed with COVID-19 ¹²⁶. Early aspirin prescription may be associated with lower odds of in-hospital mortality among hospitalized patients with moderate COVID-19 in 2,446,650 COVID-19-positive patients. The cohort screened 189,287 who were hospitalized and 112,269 who met study inclusion. The 28-day in-hospital mortality was substantially lower in those who received aspirin. Patients who received early aspirin did not have higher gastrointestinal hemorrhage, cerebral hemorrhage, or blood transfusion rates. The rate of pulmonary embolism, but not deep vein thrombosis, was also significantly lower in patients who received aspirin. The composite of hemorrhagic complications did not occur more often in those receiving aspirin. The subgroups of patients older than 60 years and patients with comorbidities appeared to benefit ¹²⁷. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized COVID-19 patients.

2. Dexamethasone Treatment Metabolism

Dexamethasone is 1-dehydro-9 α -fluoro-16 α -methylhydrocortisone or 9 α -fluoro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione ¹²⁸. It is a synthetic pregnane corticosteroid and derivative of hydrocortisone (cortisol), and it is one of the essential medicines on the World Health Organization's (WHO) list. Its stereoisomer, betamethasone, differs only in the methyl group's spatial configuration at position 16 ¹²⁹. Dexamethasone is used to treat the emetic effects of cancer therapy and epicondylitis, and it has anti-inflammatory effects ¹³⁰. It has been used to treat rheumatic problems, several skin diseases, a variety of allergies, asthma, other lung diseases, and brain swelling to improve outcomes for neonates after preterm labor and as a direct chemotherapeutic agent or in combination with other chemotherapeutic drugs in certain hematological malignancies, especially in the treatment of multiple myeloma, to counteract the development of edema in metastatic brain tumors and COVID-19 that requires supplemental oxygen (without ventilation) or mechanical ventilation ¹³¹. Dexamethasone use resulted in lower 28-day mortality among those receiving IMV or oxygen alone at randomization but not lower among those receiving no respiratory support in patients hospitalized with COVID-19 ¹³².

The Infectious Diseases Society of America (IDSA) and the European Medicines Agency (EMA) endorsed the use of dexamethasone in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require additional oxygen therapy ¹³³. In addition, low-dose dexamethasone reduced mortality in patients hospitalized with COVID-19 who required respiratory support ¹³⁴. Oncologists ubiquitously use dexamethasone for cancer patients undergoing chemotherapy. It often counteracts the specific side effects of antitumor treatments ¹³⁵. Determining how much and when to use dexamethasone, considering safety, are essential in the current pandemic.

COVID-19 has been associated with the preferential expansion of interferon (IFN^{active}) and prostaglandin (PG^{active}) neutrophil states. The SARS-CoV-2-induced gene PTGS2, encoding COX-2, is expressed in human cells and mice ¹⁰⁰. Dexamethasone expanded immunosuppressive immature neutrophils and remodelled cellular interactions by changing neutrophils from information receivers into information providers. In addition, dexamethasone affected circulating neutrophils, altered IFN^{active} neutrophils, downregulated interferon-stimulated genes and activated IL-1R2⁺ neutrophils during severe COVID-19 ¹³⁶. SARS-CoV-2 infection also induces COX-2 expression, indicating that NSAIDs (which inhibit COX-2) could modulate COVID-19 severity by reducing the production of neutralizing antibodies and inflammatory cytokines ¹⁰⁰. Aspirin can directly acetylate cGAS and suppress cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)-mediated type I interferonopathies. As a result, aspirin efficiently inhibits cGAS-mediated immune responses ¹⁰¹.

Global neutrophil expression as well as the expression of neutrophil state-specific markers, such as interferon response genes (interferon-induced transmembrane protein 1

(IFITM1), radical S-adenosyl methionine domain containing 2 (RSAD2), interferon-inducible protein 6 (IFI6) and IFN-stimulated genes 10 (ISG10)), was higher in COVID-19 neutrophils. In addition, COVID-19 neutrophils followed different maturation paths compared to bacterial ARDS neutrophils, culminating in three distinct terminal states: IFN^{active}, PG^{active}, and bacterial ARDS enriched ¹³⁶. An IFN^{active} state was characterized by IFITM1, IFITM2 and IFI6 expression: from an immature state to an IFN^{active} state characterized by IFITM1, IFITM2 and IFI6 expression and the activation of type I IFN signalling pathways with notable increases in Prostaglandin E receptor 4 (PTGER4) and PTGS2 (or COX2), which encode a proposed target in COVID-19. However, the lineage relationship was unclear for COVID-19-enriched PG^{active} clusters in COVID-19 ¹³⁶.

Neutrophil IFN responses during infections are generally considered homogenous with a uniform proinflammatory capacity, and neutrophil state-specific markers such as interferon response genes (IFITM1, RSAD2, IFI6 and ISG10) are more highly expressed in COVID-19 neutrophils ¹³⁶. The most prominent discriminating features of dexamethasone treatment were the upregulation of interleukin-1 receptor type II (IL1R2), which encodes a decoy receptor that sequesters IL-1, and the downregulation of IFITM1. Dexamethasone attenuated the neutrophil expression of IFN pathways more broadly, including reducing IFITM1-IFITM3, IFIT1, ISG15 and RSAD2 ¹³⁶. Steroid administration was associated with increased circulating immature neutrophils. Due to the repatterning of annexin signalling, immature neutrophils increased by a 2.4-fold expansion after dexamethasone treatment. Patients treated with dexamethasone shifted the neutrophil state compositions ¹³⁶.

The exact incidence of dexamethasone's adverse effects is unknown, but of the 464 patients without a prior diagnosis of diabetes mellitus, 52 (11%) developed hyperglycemia ¹³⁷. Dexamethasone is a broadly used glucocorticoid anti-inflammatory drug to regulate systemic and pulmonary inflammation progression in sepsis and ARDS via downregulation of NF-κB activity ¹³⁸. It significantly decreased NF-κB and IL-8 in the cytoplasm and nuclei of mononuclear cells after the initiation of dexamethasone therapy ^{139,140}. Nonetheless, dexamethasone treatment did not modify pathological neutrophil priming and NET production: there was no significant difference in NET production or the phenotypic landscape of circulating neutrophils after treatment with dexamethasone, either early (admission) or later (day seven during ICU admission) ¹⁴¹.

These data represent an essential avenue for further therapeutic development (e.g., NET-targeted or inflammasome or cGAS-STING therapies) in the fight against COVID-19 ARDS.

3. Dapsone Treatment

Dapsone is a small molecule with anti-inflammatory, immunosuppressive, antibacterial and antibiotic properties. Dapsone passes through the blood–brain barrier (BBB) ^{142,143}, and cotreatment with high-dose sulfadiazine results in an effective CSF concentration in humans ¹⁴⁴. The solubility of dapsone varies over a wide range depending on the solvent used (e.g., 0.2 mg/mL in water and 52 mg/mL in methanol). Therefore, dapsone has been considered a difficult-to-handle compound for experimental investigations, especially in living-cell assays ¹⁴⁵, although it is very soluble in dimethyl sulfoxide. According to the inflammasome competitor thesis ¹⁴⁶, dapsone must reach an appropriate concentration to have a protective effect. After ingesting 50–300 mg doses of dapsone, maximal serum concentrations of 0.63–4.82 mg/L have been achieved ¹⁴⁷. Moreover, the dapsone dose was increased to 200 mg daily because SARS-CoV-2-activated inflammasomes and dapsone compete for DNA binding at the molecular level [154]. Our work corroborates a finding reported in 1994 that DDS and indomethacin are weakly inhibitory (10^{-4} M range) therapeutic agents in AD ¹⁴⁸. Dapsone does not modulate NF- κ B and downregulates caspase-1 and IL-1 β in an experimental model ¹⁴⁹. However, dapsone decreases pro-IL-1 β and reduces the mature form of IL-1 β , and this regulation is accomplished at the transcriptional level ^{146,150}. This finding indicates that inflammasome complex activity itself is not directly targeted by dapsone. Moreover, dapsone regulates NLRP3 inflammasome activators and a common signalling pathway ¹⁴⁶.

Dapsone might modulate the neuropilin pathway

SARS-CoV-2 evokes a response that requires the robust induction of a subclass of cytokines, including type I and, obviously, type III interferons and a few chemokines, as occurs in response to influenza A virus, particularly respiratory syncytial virus ^{21,34}. MDIG is an essential regulator of NRP1 and NRP2, similar to SARS-CoV-2 receptors. The expression of ACE2 and NRP1 has been observed in various tissues and organs in the human body ⁶⁹. NRP1 is a tissue-specific marker of lung ILC2s, and TGF β 1–NRP1 enhances ILC2 function. NRP1 is a tissue-specific regulator of lung-resident ILC2s ⁸⁰.

Kanwar. et al. [158] administered standard treatment plus dapsone for COVID-19 ARDS patients in the intensive care unit (ICU) from December 21 to December 29, 2020. The case-control study in the ICU was symmetrical (22/22).

(Table 2).

The treatments were administered to patients with decreased FIO₂ (fraction of inspired oxygen) and no further progression of hypoxia. The results were statistically significant

according to the chi-square test and Fisher's exact test for the criteria for the effectiveness of dapsons.

Statistics 1: Chi-squared test for ARDS onset and mortality

The mortality rates at the ARDS-onset stage were 5.9% and 40%, respectively. The 17 participants at the ARDS-onset stage who received the dapsons intervention ($M = 1.7$, $SD = 2.63$) were compared to the 20 participants in the control group ($M = 2.8$, $SD = 3.79$). None died except for one patient who did not take dapsons after relapse in the dapsons-administered group. Eight of the twenty ARDS-onset patients who received standard treatment without dapsons died. A chi-square test was performed to analyze the mortality relationship between ARDS onset with dapsons and ARDS onset without dapsons. The chi-square statistic was 5.81, and the p -value was 0.016 (significant at $p < 0.05$). The group with ARDS onset treated with dapsons was more likely to survive than those with ARDS onset not treated with dapsons.

(Table 3)

Statistics 2. The chi-square statistics and Fisher's exact test

The comparison was made presuming that only the decreased FIO_2 was significant in the entire dapsons-administered (+) and nonprescribed (-) groups, which applied to only the ARDS-onset stage.

(Table 4)

The dapsons trial group was significant at the ARDS onset and aggravation stages. Dapsons resulted in surprisingly rapid clinical improvement within 24–48 hours. We could explain the respiratory failure and high death rate of the COVID-19 ARDS patients and the sudden recovery of ARDS-onset patients after taking dapsons with standard treatment: the brainstem is involved, especially the pre-Bötzinger complex, which is affected by SARS-CoV-2 inflammasomes.

Pulmonary fibrosis is a common sequela in some COVID-19 survivors and contributes to ARDS in COVID-19 patients. MDIG is elevated in pulmonary fibrosis and is a critical factor in developing lung fibrosis associated with COVID-19, chronic bronchitis, pneumonia, and cancer ⁷⁶. We analysed the complete overall analysis of the risk of death or discharge to long-term acute care hospitals or the chance of being discharged home.

Statistics 3. Dapsons offers benefits in the overall complete analysis set

In the overall complete analysis, the median age was 64 years, men were 58%, and women were 42%. The most common risk factors for deteriorating hypoxia and death were

CRP data over 150 (in 45%) and oxygen requiring >10 L/min on admission (37%). By specific measures such as initial CRP and oxygen, patients group with dapsone were not less sick than those in the control group. Sixteen of thirty patients with dapsone were discharged home requiring less than 8 L oxygen/min—mostly not more than 5 L oxygen/min; only 6 of 30 patients without dapsone were discharged home ($p < 0.001$). This analysis showed a lower risk of death or discharge to long-term acute care hospitals (RR = 0.52, 95% CI: 0.32 to 0.84) and a higher likelihood of discharge home (RR = 2.7, 95% CI: 1.2 to 5.9) with dapsone compared to those receiving the usual standard of care without dapsone ¹⁵¹.

Dapsone might feature as an NRP1 regulator in the view of its therapeutic mechanisms and as a potential preventive medicine for COVID-19 ARDS in the view of clinicians.

The molecular properties of dapsone competitively inhibit inflammasomes.

Neutrophils within the pulmonary microvasculature of serious COVID-19 are associated with widespread neutrophil extracellular traps (NETs). The systemic immune response in COVID-19 ARDS patients is dominated by a unique neutrophil landscape distinct from non-COVID ARDS. Sera from patients with COVID-19 have elevated levels of cell-free DNA, myeloperoxidase (MPO)-DNA complexes, and citrullinated histone H3. Cell-free DNA and MPO-DNA were high in hospitalized patients receiving mechanical ventilation or breathing room air ¹⁴¹. Dapsone binds to myeloperoxidase and regulates the hypochlorite production from NETs. It increases cell survival from MPO-DNA NETs ^{146 89 151}. The nucleophilic/electrophilic zone of dapsone interacts with amino acids by molecular bonding. Neurotoxicity, aggregation, and free-radical formation are initiated by the methionine (Met) residue at position 35 in the A β C-terminal domain ¹⁵²⁻¹⁵⁴. The two-electron oxidation of bicarbonate is mediated by hydrogen peroxide when the production of peroxydicarbonate (HCO_4^-). The bicarbonate/carbon dioxide pair accelerates one-electron oxidation. Carbonate-radical anions ($\text{CO}_3^{\bullet-}$) mediate one-electron reactions that promote one-electron oxidation that efficiently oxidizes Met residue thioester sulfur to radical sulfur cations ($\text{MetS}^{\bullet+}$) ¹⁵⁵. Dapsone has a structure that can competitively reduce positively charged sulfur radical production because it is similar to methionine sulfoxide ¹⁴⁶. The reversal of protein ubiquitylation was the subject of our study. The ability for ubiquitination to be reversed by deubiquitinating enzymes (DUBs) serves as an important regulatory layer within the ubiquitin (Ub) system. The human genome encodes approximately 100 DUBs, and DUBs are implicated in pathologies, including neurodegeneration and cancer ¹⁵⁶. The conjugation of Ub can be reversed by DUBs and reflects additional regulation of ubiquitin ¹⁵⁷. The covalent attachment of Ub to substrates has generated dapsone capable of competing with pathogenic targets in Ub-conjugating targeting chimeras ^{146,158}. The nucleophilic properties of dapsone facilitate its competition with Ub, which is similar to DUBs. Prior to loading Ub onto the substrate, the Ub-activating (E1)/Ub-conjugating

(E2)/E3 ligase act out at each point of the ubiquitination process. Enzymes can carry Ub via a thio-ester linkage, allowing the vigorous favorable attack of the substrate nucleophile. Dapsone competitively inhibits the ubiquitination cascade. A same mechanism can potentially ubiquitinate cysteine thiols and hydroxyls on serines, threonines, leucines, and tyrosines^{146,156}. Dapsone noncovalently binds/interacts with the minor groove of DNA. The dapsone–DNA interaction/binding relative binding energy is $-6.22 \text{ kcal mol}^{-1}$, as estimated through in silico studies. Docking analysis further revealed that dapsone preferentially binds to AT-rich regions of DNA¹⁵⁹. The nucleophilic properties of dapsone also make it compete with NLRP3. ORF8b activates NLRP3 through interaction with the AT-rich repeat domain of NLRP3¹⁴⁶.

(Figure 5)

Dapsone noncovalently binds to the minor groove of DNA, and the dapsone–DNA complex may disrupt DNA replication, repair, transcription, and recombination in SARS-CoV-2 inflammasomes. Dapsone can be used to physically obstruct DNA replication in inflammasomes^{89,160}. Therefore, we defined dapsone as typical anticatalytic medicine. As stated earlier, dapsone noncovalently binds/interacts with the minor groove of DNA. The dapsone–DNA interaction/binding relative binding energy is $-6.22 \text{ kcal mol}^{-1}$, as estimated in silico studies. Docking study further revealed that dapsone better binds to AT-rich regions of DNA¹⁵⁹. The nucleophilic properties of dapsone also make it compete with NLRP3. ORF8b activates NLRP3 through interaction with the AT-rich repeat domain of NLRP3¹⁴⁶. The inflammasome pathway constitutes the primary mechanistic insight into the inextricable relationship between the COVID-19 inflammasome response, spike protein-related diseases, prion-like diseases and subsequent hematological malignancy.

Many inflammasomes are generated and interact, and the cation environment in the body is also rapidly changing. The NLRP3 inflammasome is activated in acute kidney injury, chronic kidney diseases, diabetic nephropathy, and hyperuricemic nephropathy¹⁶¹. The interplay of inflammasome mediators with immune modulators and transcription factors has a significant role in developing myeloid diseases¹⁶². COPD develops via activation of NLRP3 inflammasome-mediated pyroptosis¹⁶³. Autoinflammatory diseases are associated with aberrant cell death and inflammasome activation^{164 165}. SARS-CoV-2 induces NLRP3 inflammasome activation in the following human cells: primary human monocytes, human peripheral blood mononuclear cells (PBMCs), supernatants from PBMCs, human macrophages, human serum, postmortem lung tissue, human hematopoietic stem cells (HSCs), very small embryonic-like stem cells (VSELs), and endothelial progenitor cells (EPCs). mRNA vaccines with the full-length prefusion spike glycoprotein (S) of SARS-CoV-2 might induce NLRP3 inflammasome activation in human cells, such as SARS-CoV-2: caspase-1 activation, increased levels of IL-1 β and ASC, pyroptosis, increased lactate dehydrogenase (LDH) levels, lytic cell death, and SARS-CoV-2 S1 protein-induced nuclear factor kappa-light-chain-

enhancer of activated B-cell activation¹⁶⁶. mRNA vaccines showed hypersensitivity reactions, lymphadenopathy, appendicitis, pericarditis, myocarditis, uveitis, herpes zoster infection¹⁶⁷, and increased risk of Bell's palsy in Hong Kong¹⁶⁸, anaphylaxis, cerebral venous sinus thrombosis, thrombocytopenia, myocarditis, and pericarditis. In addition, BNT162b2 and mRNA-1273 were similar to clinical trials on anaphylaxis, a severe, life-threatening allergic reaction¹⁶⁹. Inflammasomes are a common cause of cognitive impairment in AD, arrhythmias, atherosclerosis, autoimmune encephalomyelitis, cardiac arrhythmias, colitis, diabetes, myocardial infarction, steatohepatitis, stroke, thrombocytopenia, traumatic brain injury^{47 150}, and inflammatory bowel disease¹⁷⁰. The SARS-CoV-2 inflammasome has induced several similar diseases¹⁴⁶, and the mRNA vaccine spike protein damages human cells via the inflammasome. It can cause adverse effects and other inflammasome diseases among mRNA vaccine recipients. Barhoumi et al. reported spike protein-induced apoptosis and inflammatory and oxidative stress responses¹⁷¹. Targeting NLRP3 may activate cytokines or PAMPs induced by mRNA vaccines expressing the full-length prefusion spike glycoprotein of SARS-CoV-2. NLRP3 leads to the transcriptional upregulation of canonical and noncanonical inflammasome components¹⁵⁰. mRNA vaccine S might induce adverse reactions by inflammasomes.

(Table 5)

Dapsone competitively inhibits the ubiquitination cascade. The same mechanism can potentially ubiquitinate cysteine thiols and hydroxyls on serines, threonines, leucines, and tyrosines^{146,156}. Dapsone might competitively inhibit K27-linked ubiquitination on K384 of cGAS, inhibiting cGAS activity in response to RNA-virus infection. The best-defined sites are the amine-containing internal lysine residues along with the free amine of N-terminus in the polypeptide backbone. Ub is activated by E1 enzyme, using energy from ATP hydrolysis, and passes to a Ub- E2 enzyme. Ub can then be moved to a substrate protein, specified by the distinct E3 ligase that binds both the substrate and the E2. K384 and K414 of cGAS are critical residues for cGAS regulation by multiple PTMs. cGAS undergoes K48-linked ubiquitination at K414, leading to the p62-dependent selective autophagic degradation of cGAS in resting cells, and upon DNA virus infection, this inhibitory ubiquitination is removed, promoting cGAS activation¹¹⁰. Acetylation on K414 may compete with ubiquitination to maintain an appropriate level of cGAS protein in resting cells, and K27-linked ubiquitination on K384 of cGAS has been shown to potentiate cGAS activity in response to DNA-virus infection¹¹².

Dapsone treats viral respiratory diseases from 2005 to 2020 on Sorok Island

Lee et al.¹⁸ observed preventive treatment effects for dapsone, which functions as an inflammasome competitive inhibitor in pandemic viral inflammasomes. The study analysed the medical records of Sorokdo National Hospital from 2005 to 2020 to study the targeting of the

NLRP3 inflammasome by dapsone. Leprosy patients who had lived on Sorok Island for a lifetime were analysed. According to the information from 2005 to 2020 on October 27, 2020, a total of 2186 individuals (1152 males and 1034 females) resided, and the average age was 83.7 years (median (M), 84; interquartile range (IQR), 76.8~91.2; standard deviation (SD), 10.8; 95% confidence interval (CI), 0.45, 83.6~84.5). The 3705 VRD participants who received the dapsone intervention compared to the 1172 VRD participants in the control group demonstrated T2 (M = 269.88, SD = 88.70, 95% CI 266.13-273.62, p-value < .00001):T3 (M = 59.75, SD = 93.36, 95% CI 51.36-68.14, p-value < .00001) definitely proves that VRD is very low when dapsone is taken, and very high when not taken. The t-value is -3.42, and the p-value is 0.0014. (significant at $p < 0.05$). It demonstrated significantly more prevalence of VRD in the DDS unprescribed group¹⁸.

(Figure 6)

Lee et al. also designed the Factor consisting of the dapsone taking group and anti-Alzheimer's disease drug (AAD) taking Alzheimer's disease (AD) diagnosed group, and it was strongly negatively correlated with the prevalence of Bronchitis and chronic obstructive pulmonary disease (COPD). Our calculations from Spearman's Rho (rs), the association between Bronchitis and Factor was statistically significant: the value of rs is -0.83929. $rs = -0.83929$, p (2-tailed) = $9E-05$. The association between COPD and Factor was statistically significant: the value of rs is -0.83929. $rs = -0.83929$, p (2-tailed) = $9E-05$. However, the association between Pneumonia and Factor would not be considered statistically significant: the value of rs is -0.38571. $rs = -0.38571$, p (2-tailed) = 0.15563. It means that dapsone treated both, and AAD exacerbated both, but the Factor had nothing to do with Pneumonia. Dapsone should attenuate VRDs, Bronchitis and COPD, but AAD exacerbate Bronchitis and COPD¹⁸.

The potential efficacy of dapsone in treating COVID-19-related illness was shown through a reduction in the impact of COVID-19 and its symptoms among Hansen's disease (HD) patients in South Korea treated with state-supplied dapsone at 100 mg daily. They made dapsone accessible to all leprosy patients (dapsone, 100 mg—1000 tablets/bottle, for 3814 of 9134 leprosy patients). They reported that HD patients in South Korea had no reports of outbreaks of respiratory infectious diseases between 2002 and 2021.04.30¹⁴⁶. Dapsone has been linked to the regulation of mild cognitive impairment, Alzheimer's disease^{146,172,173}, and SARS-CoV-2-associated ARDS⁸⁹.

Judging from such therapeutic effects by dapsone, the downstream IFN stimulated cascade with anti-IFN γ signaling in the onset stages of disease must attenuate the overactive immune-mediated respiratory inflammatory diseases where NRP1 is abundant^{33 71 72 80}.

Assessment

COVID-19 has revealed a network of metabolic trajectories aligned with multiple pathways for immune activation with clinical, cellular, molecular, and immunological severity scales regarding organ damage. While an immune response is necessary for clearing SARS-CoV-2 infection and establishing immunological memory to combat reinfection, hyperinflammatory responses have also been shown to underlie the pathology of exacerbated COVID-19. Furthermore, COVID-19 therapeutic interventions could have regulated and anticatalyzed immune responses of SARS-CoV-2 in multiple ways.

We recommend anticatalytic medicines to treat or prevent diverse COVID-19 diseases induced by SAMHD1 tetramerization and cGAS–STING signalling pathway, ACE2 and TLRs pathway, inflammasomes-spike protein-genetic pathway, and innate lymphoid cells with neuropilin-1 pathway.

Conclusion

It is necessary to prescribe anticatalytic treatments as the first line of therapeutics against SARS-CoV-2.

Take-home message

The triad is effectively controlling diverse immune responses induced by SARS-CoV-2.

List of abbreviations

ACE	Angiotensin-converting enzyme
AD	Alzheimer's disease
AESI	Adverse events of special interest
AGS	Aicardi–Goutières syndrome
AMI	Acute myocardial infarction
AMI I/R injury	AMI ischaemia–reperfusion injury
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
BDNF	Brain-derived neurotrophic factor
BiPAP	Bilevel positive airway pressure
BV-2	A type of microglial cell derived from C57/BL6 mice
CAPS	Cryopyrin-associated periodic syndromes
CARD	Caspase activation and recruitment domain
CCR2	C-C motif chemokine receptor 2
CH	Clonal hematopoiesis, hematopoietic stem and progenitor cells
CI	Confidence interval
CK-MB	Creatine kinase-MB fraction
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase 2
CRP	C-reactive protein
CRS	Cytokine release syndrome

DDS	4,4'-Diaminodiphenyl sulfone (dapsone)
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
EPCs	Endothelial progenitor cells
G6PDH	Glucose-6-phosphate dehydrogenase
HLA	Human leukocyte antigen
HLA-DRB1	Major histocompatibility complex, Class II, DR beta 1
ICU	Intensive care unit
IFN	Interferon
IFNAR2	Interferon-alpha and beta receptor subunit 2
IL	Interleukin
IL-1 β	Interleukin-1 beta
IMV	intensive mechanical ventilation
IRF3	Interferon regulatory factor 3
JNK	Jun N-terminal kinases
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LL	Lepromatous leprosy
MADDS	Monoacetyldapsone
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MHC	Major histocompatibility complex
MIS-C/A	Multisystem inflammation syndrome in children and adults
MPO	Myeloperoxidase
mRNA	Messenger RNA
mtDNA	Mitochondrial DNA
NACHT	Domain conserved in NAIP, CIITA, HET-E and TP1
NF- κ B	Nuclear factor kappa light chain enhancer of activated B cells
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
PAI-1	Plasminogen activator inhibitor-1
PAMPs	Pathogen-associated molecular patterns
PBMCs	Human peripheral blood mononuclear cells
PD	Parkinson's disease
PEDF	Pigment epithelium-derived factor
PEDFR/iPLA2	PEDF/calcium-independent phospholipase A2
Phospho-p65	Anti-phospho-NF κ B p65 (Ser536) monoclonal antibody (T.849.2)
Phospho-I κ B α	Phospho-I κ B α (Ser32/36) (5A5) mouse mAb #9246
PTGS2	Prostaglandin synthase 2
PTM	Multiple posttranslational modification
ROS	Reactive oxygen species

S	Full-length prefusion spike glycoprotein of SARS-CoV-2
S1	SARS-CoV-2 spike protein subunit 1
SCLS	Systemic capillary leak syndrome
RCT	Randomized controlled trial
SOD	Superoxide dismutase
TGF- β	Transforming growth factor-beta
THP-1	A spontaneously immortalized monocyte-like cell line
TNF	Tumor necrosis factor
TLR	Toll-like receptor
TMPRSS2	Transmembrane protease serine subtype 2
TTS	Thrombosis with thrombocytopenia syndrome
TYK2	Tyrosine kinase 2
VSELs	Very small embryonic-like stem cells

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Author contributions

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Competing interest statement

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. The roles of cyclin-dependent kinase and cGAS–STING signalling

Cyclin-dependent kinase 1 (CDK1), CDK2, and CDK6 inhibit SAMHD1 antiviral function via phosphorylation and inactivation. HBV recruits cyclin E2 to bind CDK2 and further phosphorylated SAMHD1 to abrogate its restriction of HBV replication. SARS-CoV-1 suppresses the activity of the cyclin d-CDK4 and cyclin A/E-CDK2 complexes, and SARS-CoV-2 enhances the phosphorylation of CDK2 to inhibit cellular mitosis.

Pattern recognition receptors are essential in sensing pathogen-associated molecular patterns (PAMPs) and DAMPs. For example, Toll-like receptors (TLRs) recognize a variety of PAMPs and DAMPs that initiate the process of inflammation via the activation of nuclear factor (NF)- κ B and the synthesis and release of cytokines and interferons (IFNs). Inflammasomes are a distinct class of intracellularly expressed pattern recognition receptors (PRRs) that recognize nucleic acids and mediate proinflammatory responses. Cell-surface-expressed ACE2 and TLR4 increase the NLRP3 inflammasome downstream mediator caspase-1, and exposure to spike protein upregulates the protein expressions involved in the positive stimulation of TLR4 signalling and the inflammasome pathway. The induction of neuroinflammation in microglia is mediated through the activation of NF- κ B (nuclear factor-kappa B cells) and p38 MAPK (mitogen-activated protein kinase), possibly due to TLR4 activation. TLR4 has been found to play a critical role as a mediator of the neurotoxicity induced by α -synuclein oligomers. Misfolded α -synuclein (α -Syn) induces inflammatory responses, and extracellular α -Syn can activate proinflammatory TLR4 pathways in astrocytes, but α -Syn uptake is independent of TLR4. The interaction between TLR4 and SARS-CoV-2 S can trigger an intracellular TLR4 signaling cascade. NF- κ B's transcriptional activation of specific genes induces the release of proinflammatory cytokines, which can cause neuronal damage and pathological modification of α -Syn. Serum neurofilament light chain (NFL) is a specific biomarker of neuronal injury. NFL was higher in COVID-19 patients than in the control groups. Higher NFL levels were associated with neuronal injury. It is common in critically ill patients. The hyperinflammatory state of COVID-19 has high levels of proinflammatory cytokines, and it might have triggered central nervous system neuroinflammation through the activation of astrocytes and microglia, which could have facilitated prion-like pathology. In addition, similar to other prion proteins, the S-protein also contains several prionogenic domains.

Thus, direct toxic action of the spike protein, triggering a neurodegenerative condition mimicking a prion disease-like pathology, is also possible. The biological implications of nuclear cGAS and its interaction with chromatin, including various mechanisms for nuclear cGAS inhibition, the release of chromatin-bound cGAS, the regulation of different cGAS pools in the cell, and chromatin structure/chromatin protein effects on cGAS activation, could lead to cGAS-induced autoimmunity. Cytosolic DNA recognition leads to active cGAS by

clustering and forming large liquid–liquid phase-separated cGAS–DNA condensates, excluding the ER-directed exonuclease three-prime repair exonuclease 1 (TREX1). Nuclear cGAS is sequestered at chromatin in an inactive state. Active cGAS produces cyclic GMP-AMP (cGAMP), which binds to STING. STING relocates to the perinuclear Golgi and forms a clustered platform where the TBK1 kinase phosphorylates the transcription factor IRF3. Phosphorylated IRF3 enters the nucleus and, along with NF- κ B, triggers the expression of type I interferon and proinflammatory cytokine genes.

(Reproduced from de Oliveira Mann CC, Hopfner KP. Nuclear cGAS: guard or prisoner? *EMBO J.* 2021 Aug 16;40(16):e108293. doi: 10.15252/embj.2021108293. Epub 2021 Jul 12. PMID: 34250619; PMCID: PMC8365253.)

[HBV, hepatitis B virus; P, phosphate; The green arrows mean enhancement, and the dashed arrow means the effect is uncertain: CDK, cyclin-dependent kinase; SAMHD1, Sterile alpha motif histidine-aspartic acid domain-containing protein 1]

Figure 2. Innate lymphoid cells and neuropilin 1

Innate lymphoid cells (ILCs) comprise non-T, non-B, lymphoid cells in humans, and they can be divided into three groups based on distinct cytokine profiles and the transcription factors. Group 3 ILCs (ILC3s), which are dependent on the transcription factor retinoic acid-related orphan receptor-gamma t (RORγt), are present in lymphoid tissues. ILC3s produce higher amounts of cytokines than ILC3s without neuropilin 1 (NRP1). Neuropilin-1 (NRP1)+ ILC3

cells present at high frequencies in fetal tissues and ectopic lymphoid aggregates in patients with chronic lung disease, suggesting their potential role in inflammation and vascularization. NRP1, which is induced postnatally and sustained by lung-derived transforming growth factor beta-1 (TGFβ1), is a tissue-specific marker of lung Group 2 innate lymphoid cells (ILC2s). TGFβ1–NRP1 signaling enhances ILC2 function and type 2 immunity, which identifies NRP1 as a tissue-specific regulator of lung-resident ILC2s and features an NRP1 regulator as a potential therapeutics for pulmonary fibrosis.

Figure 3. The immune-to-brain communication

The perivascular space contains of a single or double layer of invaginated pia in the brain, forming an interstitial fluid-filled space representing an extension of the extracellular fluid space around the intracranial vessels as they move down into the brain parenchyma. Human sensory stimuli affect the breathing sensation passing through the cerebral cortex and hypothalamus. The respiratory muscles are not purposely activated in healthy breathing. Neuropilin-1 (a pleiotropic single-transmembrane coreceptor for class-3 semaphorins and vascular endothelial growth factors) has been confirmed as a coreceptor that facilitates SARS-CoV-2 infection into cells and may be expressed in the brainstem. Activated microglia were observed in the olfactory bulb, midbrain (particularly, in the substantia nigra), hindbrain, dorsal motor nucleus of the vagus nerve, and pre-Bötzinger complex in the medulla. Neuroinflammation with microgliosis and T-cell infiltration in COVID-19 brains was significantly greater than that in patients who did not have COVID-19. This might trigger inflammasomes and pyroptosis in the CNS. Brainstem involvement, especially pre-Bötzinger complex involvement, could account for the respiratory failure and sudden high death rate of COVID-19 ARDS patients. The neurovirulent potential of SARS-CoV-2 is not restricted to patients with mild or severe diseases that can develop neurological complications. Microglia and astrocytes play specific and dynamic roles during immune activation. This immune-to-brain communication occurs when glia, microglia, and astrocytes interpret and propagate inflammatory signals in the brain and influence physiological and behavioral-change responses. Activating the peripheral immune system with a coordinated brain response elicits and influences physiological and behavioural responses in the immunological memory engram pathway.

Figure 4. Aspirin strongly inhibited cGAS-mediated TBK1–IRF3 signalling.

The sensing of cytosolic DNA by the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) is central to the pathogenesis of several autoinflammatory syndromes and some autoimmune diseases like systemic lupus erythematosus (SLE) because the presence of DNA in the cytoplasm is usually a sign of microbial infections and is quickly detected by cGAS, eliciting anti-infection immune responses. However, the chronic activation of cGAS by self-DNA leads to severe autoimmune diseases for which no effective treatment is yet available. The activation of cGAS signalling

requires its deacetylation, while acetylation inhibits cGAS activation, and the compulsory acetylation of cGAS by aspirin forcefully suppresses self-DNA-induced autoimmunity, giving aspirin therapeutic potential in this context.

Recently, the unique role of cGAS—stimulator of interferon genes (STING) pathway in orchestrating innate and adaptive immunity has led to vast interest in employing antagonists of the cGAS–STING pathway as SARS-CoV-2 therapeutic adjuvants. The DNA sensor cGAS detects pathogenic or cytosolic nucleic acids and produces the second messenger, 2'3'-cGAMP, which binds to STING. Activated STING dimerizes and translocates from the endoplasmic reticulum (ER) to the Golgi apparatus. STING is ubiquitinated at the Golgi apparatus, an anchor for tank-binding kinase 1 (TBK1). Stimulation of the cGAS–STING pathway by cytosolic nucleic acids can activate interferon regulatory factor 3 (IRF3) and nuclear factor- κ B (NF- κ B) and promote the transcription of type I interferons (IFNs) and other proinflammatory cytokines, modulating antigen presentation and immune responses. Therefore, cGAS–STING antagonists are promising adjuvants for constructing effective SARS-CoV-2 therapeutics. Acetylation inhibits cGAS activation, and enforced acetylation of cGAS by aspirin robustly suppresses self-DNA-induced autoimmunity. Aspirin inhibited cGAS-mediated interferon production¹⁰¹.

Figure 5. Treatment mechanisms of dapsone.

Dapsone binds to myeloperoxidase and regulates hypochlorite production, reducing cellular content. The topologic properties of dapsone, such as its electron density and Laplacian delocalization index, and the negative potential of the neighborhood of O and O atoms result in susceptibility to severe electrophilic attack. The nucleophilic/electrophilic sector of dapsone interacts with amino acids by molecular bonding. Dapsone has a structure that can reduce the production of sulfur radicals by electron transfer because it is structurally similar to methionine sulfoxide. The dapsone–DNA interaction/binding relative binding energy is $-6.22 \text{ kcal mol}^{-1}$, as estimated in silico studies. Docking study further revealed that dapsone favourably binds to the AT-rich region of DNA. The nucleophilic properties of dapsone also make it compete with NLRP3. ORF8b activates NLRP3 through interaction with the AT-rich repeat domain of NLRP3 (86) Proteins contain many nucleophilic sites able to attacking a ubiquitin (Ub)-conjugating enzyme (E2)–Ub thioester linkage and undergoing ubiquitination. The best-labeled sites are the amine-containing internal lysine residues and the free amine in the polypeptide backbone's N-terminus. Ub is stimulated by a Ub-activating (E1) enzyme, using energy from ATP hydrolysis, and goes to a Ub-conjugating (E2) enzyme. Ub can then be passed to a substrate protein, specific the distinct E3 ligase that binds both the substrate and the E2. Thus, dapsone can compete with the ubiquitination cascade.

Figure 6. Dapsone treatment study.

Sorok Island, a Japanese Leper colony, was established in May 1916 for quarantined leprosy patients. South Korea declared war against dementia in 2008 and planned a National Dementia Plan every five years. The Korean National Assembly unanimously passed the Dementia Management Act in 2011, which was enacted to diagnose and treat all Hansen subjects for Alzheimer's disease without exception. According to the Dementia Management Act, the medical staff of Sorokdo National Hospital began a full examination in 2011 for the treatment of dementia for all leprosy patients on Sorok Island. As a result, an anti-Alzheimer's-disease drug was prescribed for subjects diagnosed with dementia, and doctors stopped prescribing dapsone for inactive leprosy patients. All treated leprosy patients have been followed up since 2011. The Dementia Management Act administered dapsone to the trial group if one classified the subjects not prescribed dapsone as the control group. Medical data on the connection between dapsone and viral respiratory diseases were analysed, but SARS-CoV, influenza A virus subtype H1N1, MERS, and SARS-CoV-2 did not occur from 2002 to 2020. Therefore, we studied more detailed international Classification of Diseases (ICD) codes for respiratory infectious diseases (RIS): acute nasopharyngitis (J00); acute sinusitis (J01); other acute sinusitis (J01.8); acute pharyngitis (J02); acute pharyngitis, unspecified (J02.9); acute tonsillitis (J03); streptococcal tonsillitis (J03.0); acute tonsillitis, unspecified (J03.9); acute laryngitis (J04.0); acute laryngopharyngitis (J06.0); acute upper respiratory infection, unspecified (J06.9); influenza due to identified zoonotic or pandemic influenza virus (J09); influenza with other manifestations, seasonal influenza virus identified (J10.8); viral pneumonia, unspecified (J12.9); other bacterial pneumonia (J15.8); bacterial pneumonia, unspecified (J15.9); bronchopneumonia, unspecified (J18.0); pneumonia, unspecified (J18.9); acute bronchitis, unspecified (J20.9); chronic rhinitis, nasopharyngitis and pharyngitis (J31); chronic rhinitis (J31.0); chronic nasopharyngitis (J31.1); chronic pharyngitis (J31.2); chronic sinusitis (J32); chronic pansinusitis (J32.4); other chronic sinusitis (J32.8); chronic tonsillitis (J35. 0); and chronic laryngitis (J37.0). Treatment one was a dapsone-prescribed (+) with VRD-diagnosed (+) subgroup, and the other was a dapsone-nonprescribed (-) VRD (+) subgroup. The 3022 participants who took dapsone were compared to the 3961 who did not prescribe it. Two trendlines demonstrated a significantly greater prevalence of viral respiratory disease in the dapsone (-) group and vice versa.

Study Result of T2:T3

■ T2: VRD(+)/DDS(-) - $92.1 + -3.15x + 6.27x^2 + -0.364x^3$ $R^2 = 0.967$

■ T3: VRD(-)/DDS (+) - $235 + 18.7x + -8.43x^2 + 0.432x^3$ $R^2 = 0.981$

Table 1. Epigenetically upregulated receptors/mediators associated with SARS-CoV-2 entry.

Factor	Receptor Mediator	Role in COVID-19	Histone marks in ¹ mdig ⁺ epithelial cells	Ref.
Ageing	ACE2	Age-dependent DNA methylation was observed close to the transcription start site of the ACE2 gene in airway epithelial cells. Histone modifications and the levels of histone proteins change during ageing, which dramatically influences chromatin compaction and gene expression.	↓ ³ H3K9me3 ↓ ³ H3K27me3 ↑ ³ H3K36me3 ↑ ³ H4K20me3	174 175 176 79
	DNA methylation	↑ methylation of IFN-related genes. ↓ inflammatory genes hypomethylated		96
Smoking		Epigenetic mechanisms alter the common transcriptional bridge between smoking and COVID-19 by trimethylation of particular lysine (K) residues at H3 and H4 histones.	↑H3K4me3 ↓H3K9me3 ↓H3K27me3 ↓H4K20me3	78
	ACE2	The primary receptor mediating SARS-CoV-2 entry, the expression of ACE2 is maintained, if not upregulated, due to the arsenic-induced impaired activity of ² EZH2.	↓ ³ H3K27me3	76 177 178
	⁴ NRP1	They are highly expressed in the respiratory tract epithelial cells; NRP1 bind the S1 segment of the SARS-CoV-2 spike protein following its cleavage by furin.	↑ ³ H3K4me3 ↓ ³ H3K9me3	76 74
	NRP2	Similar to NRP1.	↑ ³ H3K4me3 ↓ ³ H3K9me3 ↓ ³ H3K27me3	76 73
	⁵ AT1R	It facilitates SARS-CoV-2 entry through receptor-mediated endocytosis of ACE2-S complex following the interaction of viral spike protein with soluble ACE2.	↓ ³ H3K9me3	76 179 180
	⁶ CTSD	Potentially facilitates SARS-CoV-2 entry through positive regulation of furin through osteopontin.	↓ ³ H3K9me3 ↓ ³ H3K27me3	76 181- 183
	⁷ CTSL	Elevated in the serum of COVID-19 patients, CTSL mediates viral entry by participating in the cleavage of the viral S protein.	↑ ³ H3K4me3 ↓ ³ H3K9me3 ↓ ³ H3K27me3	76 184
	⁸ PTGER2-4	Upregulation of PGE2 receptors might potentiate the positive regulatory effect of PGE2 on ACE2 and TMPRSS2, facilitating SARS-CoV-2 entry.	↑ ³ H3K4me3	76 185,186
	⁹ SLC6A20/SIT1	Positively regulated by ACE2, SLC6A20/SIT1 is suspected of interacting with ACE2 and enhancing its activity reciprocally.	↓ ³ H3K27me3	76 187,188
	IL-6	Present in high levels in the serum of COVID-19 patients, IL-6 is speculated to enhance viral entry by activating the AT1R signalling cascade.	↓ ³ H3K27me3	180,189- 191
¹⁰ ISG	¹¹ HDAC	An ISG expression signature is a hallmark of interferonopathies and other autoimmune diseases. Combined inhibition of HDAC1/2 and ¹² BRD4 resolved the aberrant ISG expression detected in cells derived from patients with two inherited interferonopathies ⁹⁷ .	↑ ³ H3K36me3	176

¹The heterozygous mdig knockout (mdig⁺), ²Enhancer of zeste homolog 2 (EZH2) - a histone-lysine N-methyltransferase enzyme encoded by EZH2 gene that joins in histone methylation and transcriptional repression. EZH2 catalyzes the adding methyl groups to histone H3 at lysine 27 using the cofactor S-adenosyl-L-methionine. ³Neuropilin (NRP) ⁴packaging protein Histone H3 or H4 series (H3K27me3, H3K4me3, H3K9me3, H4K20me3) - an epigenetic modification to the DNA, ³Neuropilin (NRP), ⁵Angiotensin II type 1 receptor (AT1R), ⁶CTSD (Cathepsin D) encoded by the CTSD gene. This gene encodes a lysosomal aspartyl protease arranged of a protein dimer of disulfide-linked heavy and light chains produced from a single protein precursor. ⁷CTSL (cathepsin L) is a cysteine cathepsin, a lysosomal cysteine protease that plays a major role in intracellular protein catabolism. ⁸Prostaglandin E Receptor (PTGER), a prostaglandin receptor subtype, is a protein coding gene. ⁹Solute carrier family 6 member 20 (SLC6A20)/sodium-dependent amino transporter 1 (SIT1) - SIT1, the product of the slc6a20 gene. ¹⁰Interferon stimulating gene (ISG) ¹¹Histone deacetylases (HDAC) HDAC activity provides a required positive function for IFN-stimulated gene (ISG) expression. ¹²Bromodomain-containing protein 4 (BRD4) is a protein encoded by the BRD4 gene. Bromodomain-containing protein 4 is a protein that is encoded by the BRD4 gene in humans. (Reproduced from SHIRVALILOO, M. 2022. The unfavorable clinical outcome of COVID-19 in smokers is mediated by H3K4me3, H3K9me3 and H3K27me3 histone marks. Epigenomics, 14, 153-162.)

Table 2. Case–control study of COVID-19 ARDS patients in the ICU.

Categories	Dapsone-Administered (+) Group			Non-Dapsone-Prescribed (-) Group		
	Decrease in FIO ₂	Progression of hypoxia	No further progression	Decrease in FIO ₂	Progression of hypoxia	No further progression
Onset ^{*1}	7/22	0/22 (no deaths)	1/22	8/22	8/22 (8 deaths)	4/22
Aggravated ^{*2}	6/22	3/22 (3 deaths)	3/22	1/22	1/22	0/22
Severe ^{*3}	0/22	2/22 (2 deaths)	0/22	0/22	0/22	0/22
Total (22/22)	13	5	4	9	9	4

^{*1} FIO₂ (fraction of inspired oxygen) requirement via simple nasal cannulation of up to 15 L/min; ^{*2} FIO₂ administered via an HFNC (high-flow nasal cannula) of 95–100% and/or BiPAP (bilevel positive airway pressure); ^{*3} requiring mechanical ventilation. (Reproduced from Kanwar B, Lee CJ, Lee JH. Specific Treatment Exists for SARS-CoV-2 ARDS. Vaccines (Basel). 2021 Jun 10;9(6):635. DOI: 10.3390/vaccines9060635. PMID: 34200720; PMCID: PMC8229893.)

Table 3. Dapsone's effects as applicable to COVID-19 ARDS onset.

Dapsone-Administered (+)/Nonprescribed (-)	Decreased FIO₂	Others	Row Totals
Dapsone (+) onset ^{*1}	7	1	8
Dapsone (-) onset	8	12	20
Totals	15	13	28

Chi-square statistic: 5.18; *p* value:.023. The result is significant at *p* <.05; ^{*1} FIO₂ (fraction of inspired oxygen) necessity via simple nasal cannulation of up to 15 L/min. (Reproduced from Kanwar B, Lee CJ, Lee JH. Specific Treatment Exists for SARS-CoV-2 ARDS. Vaccines (Basel). 2021 Jun 10;9(6):635. DOI: 10.3390/vaccines9060635. PMID: 34200720; PMCID: PMC8229893.)

Table 4. Fisher's exact test: dapsone treats COVID-19 ARDS onset and aggravated patients.

Dapsone-Administered (+) Group	Decreased FIO₂ + No Progressive ARDS	Progressive ARDS	Row Totals
Dapsone (+) onset ^{*1} + Aggravated ^{*2}	17	3	20
Dapsone (+) severe ^{*3}	0	2	2
Total	17	5	22

Fisher's exact test statistic value: 0.043. The result is significant at $p < 0.05$. ^{*1} FIO₂ (fraction of inspired oxygen) requirement via simple nasal cannulation of up to 15 L/min; ^{*2} FIO₂ administered via an HFNC (high-flow nasal cannula) of 95–100% and/or BiPAP (bilevel positive airway pressure); ^{*3} requiring mechanical ventilation. (Reproduced from Kanwar B, Lee CJ, Lee JH. Specific Treatment Exists for SARS-CoV-2 ARDS. Vaccines (Basel). 2021 Jun 10;9(6):635. DOI: 10.3390/vaccines9060635. PMID: 34200720; PMCID: PMC8229893.)

Table 5. The manifestations of SARS-CoV-2 S, dapson, mRNA vaccine, and dapson in humans.

Clinical Manifestations	Sars-Cov-2 Symptoms ¹⁴⁶	Dapsone Adverse ¹⁴⁶	mRNA Vaccine Adverse	Inflammasome disease	Dapsone Treatment
skin vascular symptoms, lymphadenopathy, fever	violaceous macules with porcelain appearance, livedo of the trunk with chest pain and cough, violaceous macule and Raynaud's phenomenon 10 days after fever and cough, necrotic purpura in a patient treated with leflunomide and systemic steroids for rheumatoid arthritis, v. eruptive cherry angioma 21 days after COVID-19 healing of clinical symptoms, chilblain appearance and Raynaud's phenomenon in a patient with anosmia, fever and cough	“glandular fever”: i. fever, ii. lymphadenopathy, iii. generalized rash, and iv. hepatitis occurring after dapson intake rash, exanthema/erythema, erythroderma, mucosal involvement papular or exfoliative dermatitis, generalized lymphadenopathy	lymphadenopathy ¹⁶⁷	autoinflammatory diseases that are associated with aberrant cell death and inflammasome activation ^{165 192} .	Dapsone ^{192 193 194 195}
hypersensitivity reactions	SARS-CoV-2 symptoms are like a severe idiosyncratic DDS reaction characterized by the clinical triad of fever, rash, and systemic involvement, which can cause severe organ dysfunction (heart, kidney, lung, brain, etc.).	the syndrome is a severe idiosyncratic DDS reaction characterized by the clinical triad of fever, rash, and systemic involvement (most commonly of the liver and the hematologic system), which can cause severe organ dysfunction	mRNA vaccine induced the clinical triad of fever, rash, and systemic involvement ¹⁶⁷ . anaphylaxis ¹⁶⁹	Inflammasome produces immune modulators and cytokines ¹⁹⁶ .	
hematology laboratory	focal fibrin clusters mixed with mononuclear inflammatory cells, decreased eosinophils, decreased lymphocytes, increased neutrophils, lymphopenia, leukocytosis, neutrophilia, thrombocytopenia	leukocytosis, eosinophilia, resembling a mononucleosis infection	thrombocytopenia ¹⁶⁹	thrombocytopenia ⁴⁷	Dapsone ^{197 198}
anemia	thrombocytopenia, consumptive coagulopathy	hemolytic anemia and methemoglobinemia		the interplay of inflammasome mediators with immune modulators and transcription factors to have a significant role in	

				the development of myeloid diseases ¹⁶²	
liver disease, pancreatic disease	clinically significant liver injury is uncommon, pancreatic cells highly express ACE2	hepatitis/liver toxicity, cholangitis, colitis, thyroiditis, pancreatitis and pleural effusion	appendicitis ¹⁶⁷	steatohepatitis, colitis, diabetes ⁹ , Inflammatory bowel disease ¹⁷⁰ ,	
renal disease	severe collapsing focal segmental glomerulosclerosis, acute tubular necrosis	acute renal failure		NLRP3 inflammasome is activated in acute kidney injury, chronic kidney diseases, diabetic nephropathy, and hyperuricemic nephropathy ¹⁶¹ .	
cardiac disease	acute myocardial injury and chronic damage to the cardiovascular system	myocarditis, dapsone-induced hypersensitivity syndrome-associated complete atrioventricular block, myocardial injury	myocarditis, and pericarditis ¹⁶⁹	arrhythmias, atherosclerosis, myocardial infarction ¹⁹⁹ .	Dapsone ¹⁷³
pulmonary disease	coronavirus disease (COVID-19)-related pneumonia	pneumonitis, pneumonia or multiple organ failure	Overall increased risk of Bell's palsy in Hong Kong ¹⁶⁸	chronic obstructive pulmonary disease development via activation NLRP3 inflammasome-mediated pyroptosis ¹⁶³	Dapsone ⁸⁹
neurologic disease	ischemic stroke, Neurological complications range from potentially fatal encephalopathy and stroke to the onset of headaches and dizziness	recovery of dementia syndrome following treatment of brain inflammation	cerebral venous sinus thrombosis ¹⁶⁹	cognitive impairment in Alzheimer's disease, autoimmune encephalomyelitis, stroke, traumatic brain injury ¹⁹⁶ .	Dapsone ^{172 173 200}
others			uveitis, Herpes zoster infection ¹⁶⁷		

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