Review

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Posted Date: 31 July 2025

doi: 10.20944/preprints202507.2587.v1

Keywords: PRRs; SARS-CoV-2; COVID-19; IFNs; long COVID; TLRs

 doi:10.20944/preprints202507.2587.v1

Review

Pattern Recognition Receptors Expression and Activation in COVID-19 and Long COVID: From SARS-CoV-2 Escape Mechanisms to Emerging Immunotherapies

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is recognized by pattern recognition receptors (PRRs), which play a vital role in triggering innate immune responses such as the production of type I and III interferons (IFNs). While modest PRR activation helps to defend against SARS-CoV-2, excessive activation can cause harmful inflammation and contribute to severe Coronavirus Disease 2019 (COVID-19). Altered expression of Toll-like receptors (TLRs), which are among the most important PRR family members, particularly TLRs 2, 3, 4, 7, 8 and 9, has been strongly linked to disease severity. Furthermore, retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) — collectively known as RLRs (RIG-I-like receptors) — act as sensors that detect SARS-CoV-2 RNA. The expression of these receptors, as well as that of different DNA sensors, varies in patients infected with SARS-CoV-2. Changes in PRR expression, particularly that of TLRs, cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING), have also been shown to play a role in the development and persistence of long COVID (LC). However, SARS-CoV-2 has evolved strategies to evade PRR recognition and subsequent signaling pathway activation, contributing to the IFN response dysregulation observed in SARS-CoV-2-infected patients. Nevertheless, PRR agonists and antagonists remain promising therapeutic targets for SARS-CoV-2 infection. This review aims to describe the PRRs involved in recognizing SARS-CoV-2, explore their expression during SARS-CoV-2 infection and examine their role in determining the severity of both acute and long-term manifestations of the disease. It also describes the strategies developed by SARS-CoV-2 to evade PRR recognition and activation. Finally, given the considerable interest in modulating PRR activity as a novel immunotherapy approach, this review will describe PRR agonists and antagonists that have been investigated as antiviral strategies against SARS-CoV-2.

Keywords: PRRs; SARS-CoV-2; COVID-19; IFNs; long COVID; TLRs

1. Introduction

 doi:10.20944/preprints202507.2587.v1

Low-pathogenicity coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) circulate within the human population and typically cause mild diseases such as the common cold [1,2]. Conversely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered a highly pathogenic coronavirus. It was added to the Coronaviridae family and β-coronavirus (β-CoV) genus in 2020, alongside SARS-CoV-1 and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) [3]. The recent global pandemic, known as 'Coronavirus Disease 19 (Covid-19)', was caused by SARS-CoV-2, which resulted in millions of deaths and overwhelmed health systems [4]. Although the widespread use of anti-spike (S) vaccines has helped control the severity of SARS-CoV-2 infections, new variants of the virus continually emerge. These variants pose a particular risk to vulnerable individuals, such as the elderly and those with weakened immune systems, as they can lead to severe illness and death [5]. It has been demonstrated that the dysregulation of interferon (IFN) responses, coupled with a potent cytokine storm, are pivotal immunopathogenic mechanisms that can result in severe SARS-CoV-2 infection outcomes [6]. The recognition of SARS-CoV-2 by various pattern recognition receptors (PRRs) in the innate immune system triggers the production and secretion of type I and type III IFNs (IFN-I and IFN-III) [7], the release of inflammatory cytokines and the promotion of inflammatory cell death [6]. This results in a cytokine storm and tissue damage, which can lead to the development of acute respiratory distress syndrome [8]. In order to evade the IFN response, SARS-CoV-2 interacts with PRRs and antiviral pathways. This mechanism may be crucial to the development of severe cases of the disease [9]. It has been shown that genetic variations in PRRs significantly impact the immune response to SARS-CoV-2, favoring the progression and severity of the infection [10–14]. In this scenario, a single nucleotide polymorphism in the Toll-like receptor 3 (TLR3) gene has been linked to the severity of COVID-19 [15]. Furthermore, X-linked recessive TLR7 deficiency, mostly found in male SARS-CoV-2 patients younger than 60 years, can be considered a genetic etiology of severe COVID-19 pneumonia, by impairing the production of IFN-I by blood plasmacytoid dendritic cells (pDCs) [13]. Additionally, TLR7 represents a potential therapeutic target in controlling the infection in the early stages of the disease [13,16]. As regards, immunostimulants such as imiquimod can enhance TLR7 activation, thereby improving antiviral responses [17]. The susceptibility to and severity of outcomes from SARS-CoV-2 infection may be linked to sex-based differences, which could be explained by the location of TLR7 on the X chromosome. Men are almost twice as likely as women to experience severe outcomes, which could enhance immune responses [18]. Furthermore, the human alleles rs10774671-A and rs1131454-A have been associated with reduced levels of the 2'-5'-oligoadenylate synthetase 1 (OAS1) protein, a factor that contributes to the severity of the symptoms of the SARS-CoV-2 virus [19]. In addition to genetic variations in PRRs, anti-IFN neutralizing autoantibodies that target IFN-α/ω have been associated with reduced expression of IFN-stimulated genes and life-threatening or fatal cases of COVID-19 [20–23]. Although significant research has advanced our understanding of the characteristics, distribution and functions of PRRs, their specific role in triggering the immune response to SARS-CoV-2 remains unclear. Further investigation into PRRs-mediated responses following SARS-CoV-2 infection could lead to the discovery of new treatments for both acute [24,25] and long-term manifestations of the disease, such as long COVID (LC).

In light of these considerations, this review summarizes the dual role of PRRs in initiating and maintaining an anti-SARS-CoV-2 immune response, and their contribution to excessive inflammation and the resulting IFN cascade. Additionally, the review seeks to shed light on the strategies employed by SARS-CoV-2 to evade PRRs recognition and activation. The aim is to explore novel therapeutic strategies that target PRRs and modulate their activity in the context of long-term symptoms following SARS-CoV-2 infection.

2. The Interferon Response

Most of the available information on PRRs involved in IFN production following SARS-CoV-2 infection originates from studies on TLRs, RIG-I-like receptors (RLRs) and DNA sensors. A brief description of these groups of PRRs, along with the IFN system and pathways, can be found below.

 doi:10.20944/preprints202507.2587.v1

2.1. Pattern Recognition Receptors

Following a viral infection, pathogen-associated molecular patterns (PAMPs), such as viral nucleic acids or proteins, and danger-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), actin, and uridine diphosphate (UDP), are recognized by PRRs, thereby promoting the activation of an early antiviral immune response [26–28]. The main PRRs that play a role in inducing IFN-I and III production following viral infection are summarized in Table 1.

2.1.1. Toll-Like Receptors

A prominent group of PRRs involved in IFN induction are the TLRs. Members of the TLR family that have been shown to be involved in responses to viral infection, in part including that of SARS-CoV-2, are TLR1, TLR2, TLR3, TLR4, TLR6, TLR7, TLR8 and TLR9 (Figure 1) [29]. TLRs can broadly be divided into two categories: those located at the cell surface (TLR1, TLR2, TLR4 and TLR6) and those in the intracellular endosomal compartment (TLR3, TLR7, TLR8 and TLR9) [30]. It has been demonstrated that TLR2 interacts with several different viruses, including both DNA and RNA viruses [30]. In addition to recognizing viruses, TLR2 binds to various other exogenous and endogenous ligands, including lipopolysaccharides, lipoproteins, hyaluronic acid and heat shock protein 70 (HSP70). This activates various immune cells [31]. Following exposure to a ligand, TLR2 heterodimers activate a myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway which is shared by all TLRs except TLR3 and promotes the nuclear translocation of NF-κB. This pathway stimulates the production of inflammatory cytokines and interleukins, including tumour necrosis factor α (TNF-α), interleukin 1α (IL-1α), IL-1β, IL-6, IL-8 and IL-12 [32]. It also activates mitogen-activated protein kinases (MAPKs), which are serine/threonine-specific protein kinases that affect the transcription of inflammatory genes and stabilize mRNA by inducing activating protein-1 (AP-1) [33]. In cooperation with TLR2, TLR1 mediates the innate immune response towards lipoproteins of bacterial origin and senses the presence of viruses via their proteins [30]. TLR3 recognizes double-stranded RNA (dsRNA), which is a common intermediate in viral replication, and DNA viruses that generate dsRNA during their life cycle [34]. Following binding to dsRNA, TLR3 activates the TIR-domain-containing adapter-inducing IFN-β (TRIF) signaling pathway, resulting in the production of IFN-β and other inflammatory cytokines [35]. TLR4, the first TLR known to play a role in defending against viruses [36], recognizes a variety of ligands, including lipopolysaccharides, viral glycoproteins (mainly those of RNA viruses), necrotic cells and fibrinogen [37,38]. Although TLR6 is known to be activated by bacterial lipoproteins, recent studies have found that it can also be activated by RNA viruses and may be involved in SARS-CoV-2 infection [39–41]. TLR7 and TLR8 are two other TLRs that play a role in IFN production in response to viral infection. They recognize viral single-stranded RNA (ssRNA). They activate the MyD88-dependent signaling pathway, leading to the production of IFN-α [42]. In particular, TLR8 activates MyD88, which then recruits interleukin-1 receptor-associated kinase 4 (IRAK4) to form the Myddosome [43,44]. This complex activates IRAK1, leading to the recruitment of TNF receptor-associated factor 6 (TRAF6) and the lysine 63 (K63)-ubiquitination of IRAK1, resulting in the formation of K63/methionine 1 (M1) ubiquitin hybrids. These hybrids then activate transforming growth factor-β-activated kinase 1 (TAK1) and the IκB kinase (IKK) complexes, thereby triggering the production of pro-inflammatory cytokines via the MAPK and NF-κB pathways [45]. TLR9 binds to unmethylated cytosine-phosphate-guanine (CpG) motifs within DNA molecules. Activation of TLR9 also triggers the MyD88-dependent signaling pathway, leading to the production of IFNs [16,46,47].

2.1.2. Cytoplasmatic RNA Sensors

Another class of PRRs that are involved in IFN induction following viral infection includes retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5). RIG-I binds to short dsRNA (typically less than 1 kilobase in length) and ssRNA with 5′-triphosphate ends. In contrast, MDA5 recognizes long dsRNA typically measuring over 1 kilobase in length. Once

 doi:10.20944/preprints202507.2587.v1

viral RNA has been bound, both RIG-I and MDA5 interact with the mitochondrial antiviral signaling protein (MAVS). This triggers a signaling cascade that activates the transcription factors IFN regulatory factor 3 (IRF3) and NF-κB. This, in turn, induces the production of IFN and cytokines [48–52].

In addition to RIG-1 and MDA-5, it is also worth noting that the first cytoplasmic proteins discovered to respond to viral dsRNA molecules were the protein kinase RNA-activated (PKR) and OAS proteins [53]. The OAS family comprises the enzymes OAS1, OAS2, OAS3 and OASL. These enzymes are activated upon binding to viral dsRNAs [54]. They then activate ribonuclease L, which degrades both viral and cellular RNA. This contributes to the induction of an antiviral response and antiproliferative effects [55]. Conversely, PKRs trigger a specific translation block after binding to dsRNAs. This impedes viral replication and disrupts the cell cycle [56].

2.1.3. DNA Sensors

In addition to the above PRRs, cytosolic DNA sensors such as cyclic GMP-AMP synthase (cGAS) and absent in melanoma 2 (AIM2) are crucial in triggering the IFN response. [57,58]. AIM2 specifically recognizes cytosolic dsDNA from both mammals and viruses. This leads to the recruitment of the apoptosis-associated speck-like protein containing a CARD (ASC) in monocytes and macrophages [59]. This recruitment process forms a complex that activates caspase-1, which results in the maturation of the pro-inflammatory cytokines IL-1β and IL-18 [24,60,61]. In addition, when foreign DNA binds, the cytosolic DNA sensor cGAS catalyzes the production of cyclic GMP-AMP (cGAMP). This acts as a second messenger, activating the stimulator of interferon genes (STING) [48,62–66]. Activation of STING then triggers the downstream signaling pathways involving TANK-binding kinase 1 (TBK1) and IRF3, resulting in the production of IFN [67]. In this context, it has been proposed that STING can detect the fusion of RNA viruses with host cells and may be activated by the IFN-γ-inducible protein 16 (IFI16) inflammasome in response to host DNA damage induced by the virus [68]. The STING/TBK1/IRF pathway then enhances IFN production (Figure 1) and is thought to contribute to Kawasaki-like disease and coagulopathy in COVID-19 [69,70].

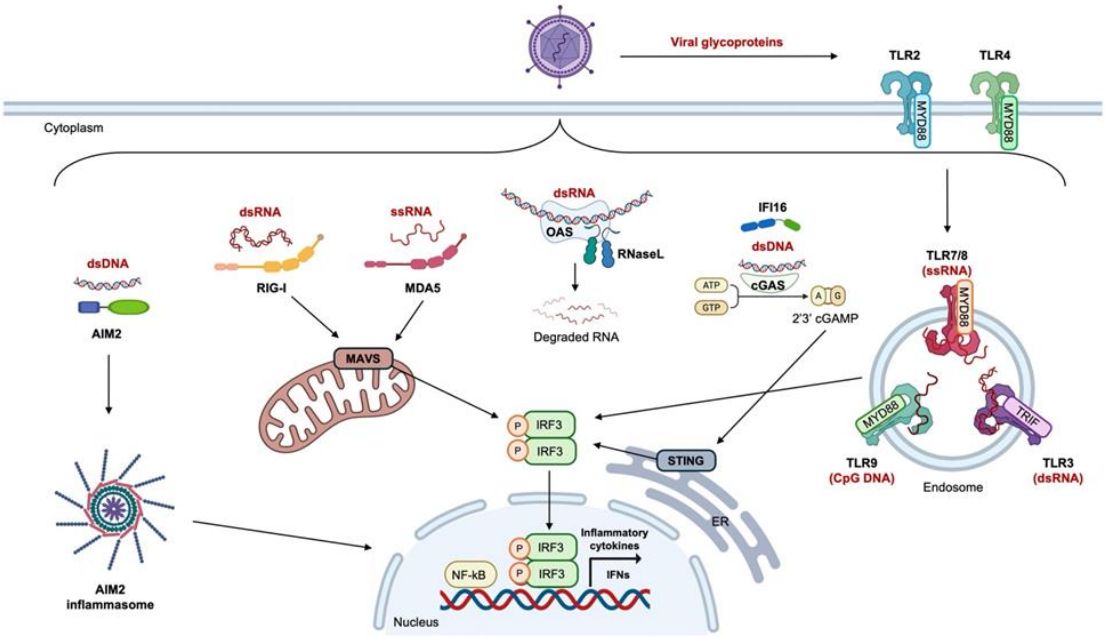

Figure 1. Key viral sensors involved in the induction of interferon production during viral infection. The figure illustrates the key viral sensors that are involved in the induction of interferon during viral infection, including membrane-bound TLRs and cytoplasmic RNA sensors (such as RIG-I, MDA5 and OAS), as well as DNA sensors (such as cGAS, IFI16 and AIM2). These sensors recognize viral nucleic acids and activate downstream antiviral signaling pathways. Abbreviations: TLRs, Toll-like receptors; RIG-I, retinoic acid-inducible gene I; MDA5,

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melanoma differentiation-associated protein 5; IFI16,Interferon gamma-inducible protein 16; AIM2, absent in melanoma 2; cGAS, cyclic GMP-AMP synthase; MAVS, mitochondrial antiviral signaling; STING, stimulator of interferon genes; OAS, 2'-5'-oligoadenylate synthetase; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; IRF3, interferon regulatory factor 3; IFN, interferon; NF-kB, nuclear factor-κB; ssRNA, single strand RNA; dsRNA, double strand RNA; dsDNA, double strand DNA; CpG DNA motifs, DNA containing the cytosine-phosphate-guanine dideoxynucleotide motif. Created with BioRender.com.

2.2. The Interferon System

In 1957, Isaacs and Lindenmann identified a cellular factor that interfered with influenza virus infection *in vitro* [71]. They named this factor 'interferon'. These findings were significant, setting the stage for further research and leading to a better understanding of the characteristics of IFN. Today, IFNs are a class of antimicrobial, antiproliferative and immunomodulatory proteins produced by most eukaryotic cells in response to various viral inducers and other stimuli. They play a pivotal role in shaping the efficacy of cellular immune responses, by enhancing the presentation of antigens to specific T cells, regulating the activity of B cells, monocytes/macrophages and dendritic cells (DCs), and fostering immune memory [72–74]. These activities have long established IFNs as antivirals, which are used in combination with ribavirin to treat chronic hepatitis C virus infection [75,76], as monotherapy for hepatitis B virus infection and to treat certain cancers and multiple sclerosis [77–80]. However, sustained or improperly regulated production of IFN during an infection can harm the host organism [81]. Consequently, host organisms have evolved sophisticated mechanisms that tightly regulate the timing and specific tissues involved in IFN production [82,83]. These mechanisms also control which pathways and genes are activated in specific cell types as part of the IFN response. The IFN family is classified into three types according to sequence, cellular origin, chromosomal location and receptor specificity [83,84]. In humans, IFN-I consists of 13 subtypes of IFN-α, as well as IFN-β, IFN-ω, IFN-ε and IFN-κ in humans (Table 1). While almost all cell types produce IFN-I, the main producers are pDCs, fibroblasts and macrophages [85–87]. IFN-II consists of only one component: IFN-γ. This is produced by activated T lymphocytes, natural killer (NK) cells and natural killer T (NKT) cells (Table 1). IFN-γ supports the function of IFN-I and is involved in regulating cell-mediated immune responses. It promotes the activation of macrophages and the presentation of antigens by inducing major histocompatibility complex classes I and II (MHC-I and MHC-II). The most recently identified class of IFNs is the IFN-III family, which includes IFN-λ1, IFN-λ2, IFN-λ3 (also known as IL-29, IL-28A and IL-28B, respectively) and IFN-λ4. These are primarily produced by epithelial cells, pDCs, myeloid dendritic cells (mDCs), neutrophils and macrophages (Table 1) [74,88–90]. This review focuses primarily on IFN-I and IFN-III because they play a crucial role in the initial innate immune response when PAMPs are recognized by PRRs. This includes responses triggered by SARS-CoV-2.

Table 1. Comparison of human type I, II and III interferons.

IFN type	Members	Main Cellular Source	Receptor	Receptor Expression	Stimuli	Chromosomal localization	References
Type I IFN	IFNα subtypes (n=13), IFNβ, IFNε, IFNκ, IFNω.	pDCs, fibroblasts, macrophages	IFNAR (consisting of two transmembrane domains, IFNAR1 and IFNAR2)	Ubiquitous expression	Microbial and viral components	Chromosome 9	[90–96]

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Type II IFN	IFNγ	NK cells, NKT cells, Th1 CD4, Tc CD8	IFNG (consisting of two transmembrane subunits R1 and R2)	Ubiquitous expression	IL-2, IL-12, IL-15 and IL-18	Chromosome 12	[48,92,93,97–100]
Type III IFN	IFNλ1, IFNλ2, IFNλ3, IFNλ4	Epithelial cells, macrophages, pDCs, mDCs and neutrophils and	IFNLR (composed of two subunits, IFNLR1 and IL10Rβ)	Epithelial cells, endothelial cells, macrophages, DCs and neutrophils	Viral and microbial components	Chromosome 19	[92,93,95,101–103]

Abbreviations: IFN: interferon; pDCs: plasmacytoid dendritic cells; NK cells: natural killer cells; NKT: natural killer T cells; Th1 CD4: T helper $CD4^+$ lymphocytes; Tc CD8: T cytotoxic $CD8^+$ lymphocytes; mDCs: myeloid dendritic cells; DCs: dendritic cells.

2.3. Type I/III Interferon and Signaling Pathways

Although IFN-I and IFN-III are genetically distinct and use different receptors, they are triggered by similar pathogen-sensing pathways and stimulate comparable gene expression programs that promote antiviral, anti-proliferative and immunomodulatory responses [103]. In particular, all IFN-I signals are transmitted via a heterodimeric receptor known as the IFN-alpha/beta receptor (IFNAR), comprising IFNAR1 and IFNAR2 subunits [104]. Conversely, IFN-III transmits signals via a heterodimeric receptor known as IFN lambda receptor (IFNLR). This receptor consists of IFNLR1 [also referred to as IL-28 receptor subunit alpha (IL28Rα)] and IL-10 receptor subunit beta (IL10Rβ) [103]. Despite having different receptors, IFN-I and IFN-III have broadly similar downstream signaling pathways and transcriptional responses. Both types activate the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, leading to the formation of the heterotrimeric transcription factor complex IFN-stimulated gene factor 3 (ISGF3). This complex consists of phosphorylated STAT1, STAT2 and IFN regulatory factor 9 (IRF9) [48]. Once activated, ISGF3 is transported to the nucleus, where it binds to IFN-stimulated response elements (ISREs). This leads to the transcription of hundreds of ISGs (Figure 2) [7,48,105]. These ISGs target the different stages of the viral life cycle and regulate various cellular processes, including protein synthesis, survival and apoptosis [7,48,106–110]. The different distribution of their receptors is a key factor in the distinct antiviral responses of IFNs. While IFNAR1 and IFNAR2 are found in almost all nucleated cells, the IFNLR complex is located on the surfaces of epithelial cells, endothelial cells, macrophages, DCs, and neutrophils [92,95,103]. As a result, the antiviral properties of IFN-III are most noticeable in the respiratory, gastrointestinal and reproductive tracts [89,102,111]. This response is also associated with the abundance of peroxisomes in epithelial tissues, as these organelles encourage the production of IFN-III rather than IFN-I in the event of MAVS signaling [112]. Furthermore, although IFN-I/III induce a largely overlapping set of ISGs, their induction kinetics and cell-type specificity differ [103]. The IFN-I response is characterized by its high potency, rapid activation and short-lived nature. This provides an immediate yet transient defense against viral infection. By contrast, the IFN-III response is generally weaker and takes longer to initiate, but provides continuous, prolonged defense. This is particularly effective at maintaining antiviral protection at mucosal and epithelial barriers [113–116]. This difference may be related to the rapid downregulation of IFN-I signaling by negative regulatory ISGs, such as ubiquitin specific peptidase 18 (USP18), ISG15 and the TAM receptors, Tyro3, Axl and Mer [117,118]. Additionally, IFN-I induce a broad response in different cell types, often resulting in a more potent inflammatory response throughout the body [73]. By contrast, IFN-III induces a more localized response, primarily in epithelial and barrier tissues. This reduces inflammation in these protective areas [103,119,120].

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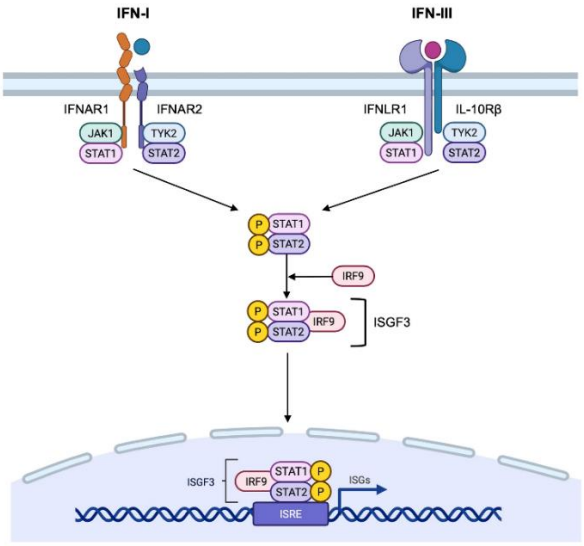
A



B

	Type I IFN	Type III IFN
Gene	Single exon	Multiple exons
Receptor binding	• Binds with high affinity to IFNAR2 • Recruits IFNAR1 with lower affinity to form a ternary complex • The receptor is ubiquitously expressed across various cell types	• Binds with high affinity to IFNLR1 • Recruits low-affinity IL-10Rβ to form a ternary complex • The receptor is expressed on epithelial cells
Response	• High potency • Rapid kinetics • Systemic effects • Inflammatory response	• Lower potency • Slower kinetics • Anatomic barriers • Less inflammatory response

Figure 2. Canonical signaling pathways of type I and type III interferons. The receptors for IFN-I and IFN-III are heterodimers, consisting of the subunits IFNAR1/IFNAR2 for IFN-I and IL28RA/IL-10R2 for IFN-III. When these receptors dimerize, they activate the kinases TYK2 and JAK1. This activation leads to the phosphorylation of STAT1 and STAT2. Phosphorylated STAT1 and STAT2 then form heterodimers that associate with IRF9 to create the transcription factor ISGF3. ISGF3 then binds to ISRE and promotes the transcription of numerous ISGs. Abbreviations: IFN-I, type I interferon; IFN-III, type III interferon; IFNAR1/2, interferon-alpha/beta receptor subunit 1/2; TYK2, tyrosine protein kinase 2; JAK1, Janus kinase 1; STAT1/2, signal transducer and activator of transcription 1/2; IRF9, interferon regulatory factor 9; ISGF3, IFN-stimulated gene factor 3; ISGs, interferon-stimulated genes; ISRE, interferon-sensitive response element. Created with BioRender.com.

2.4. Interferon Stimulated Genes

IFNs exert their cellular functions by regulating the expression of target genes, which are collectively known as interferon-stimulated genes (ISGs) [121]. These genes encode a class of proteins that primarily counteract viral infection and activate immune defenses when activated by IFN-induced pathways [122,123]. To date, almost 300 ISGs have been identified. Each of these genes plays a role in limiting viral replication and spread by performing different antiviral functions. These ISGs cover a wide range of functions, including modulation of intracellular signaling, direct antiviral defense, regulation of inflammation, and adaptation of the immune system [124–126]. However, the persistent or impaired production of ISGs and other components of the innate immune response can lead to immunopathology, resulting in damage to virus-infected mucosa [127–129].

3. SARS-CoV-2 Recognition by Pattern Recognition Receptors

Both the recognition of SARS-CoV-2 and the initiation of the IFN response are greatly influenced by PRRs [9]. Although moderate PRRs activation may offer protection, excessive activation can trigger severe inflammation [130–134] and potentially lead to serious health complications [135–138], a phenomenon that has also been observed in severe COVID-19 [139]. The primary PRRs involved in the recognition of SARS-CoV-2 are described in the following paragraphs.

3.1. SARS-CoV-2 Recognition by Toll-Like Receptors

SARS-CoV-2 is sensed by TLRs, which have been identified as critical sensors of this virus [140,141]. In this context, the following TLRs have been associated with the severity of COVID-19:

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TLR2, TLR3, TLR4, TLR7, TLR8 and TLR9 [141]. The TLRs that play a key role in recognizing SARS-CoV-2 are described below.

3.1.1. TLR2

TLR2 plays a crucial role in the immune response to SARS-CoV-2, recognizing the viral envelope protein (E) as its ligand in a specific, dose-dependent manner [142]. This sensing occurs before SARS-CoV-2 enters and begins to replicate, resulting in the release of pro-inflammatory cytokines, such as TNF-α and IFN-γ [34]. Furthermore, activation of TLR2 is linked to the formation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, thereby exacerbating the inflammatory response during SARS-CoV-2 infection [140,143]. The expression of TLR2 and MyD88 is linked to the severity of COVID-19 [34]. Furthermore, it was shown that the SARS-CoV-2 recombinant S protein interacts directly with TLR2 and TLR4 on NK cells. This activates intracellular pathways that enhance NK cell activation and control SARS-CoV-2 infection in the early stages. However, it also contributes to excessive inflammation in the later stages [144]. In particular, levels of IL-6, C-X-C motif chemokine ligand 10 (CXCL10) and granulocyte colony-stimulating factor (G-CSF) increased in wild-type (WT) mice following E protein stimulation, but not in Tlr2-/- mice or those treated with S protein [34]. Further confirmation came from the analysis of bronchoalveolar lavage fluid (BALF), which revealed that the E protein, but not the S protein, significantly increased IL-6, TNF-α, CXCL1, GM-CSF and C-C motif chemokine ligand 3 (CCL3) in WT mice [34]. Ghazanfari's study showed that the S protein induced the production of CXCL10 independently of TLR2 [145].

3.1.2. TLR3

TLR3 appears to play an initial role in SARS-CoV-2 infection by inducing IFN-α and IFN-β within the first 24 hours via IRF3. It then activates the NF-κB pathway, thereby stimulating the production of various pro-inflammatory cytokines [16]. The critical role of TLR3 is emphasized by the possibility that SARS-CoV-2 may use evasion strategies to avoid recognition of viral dsRNA by PRRs, in a manner similar to SARS-CoV-1 [146]. The study by Han et al. suggests that the SARS-CoV-2 accessory protein ORF9b hinders the production of IFN-I/III by targeting components of the TLR3-TRIF endosomal RNA-sensing pathway in vitro [147]. The complexity of the role of TLR3 also depends on the timing of its activation. The timing of TLR3 activation affects its role in initiating and maintaining immune defences against SARS-CoV-2 infection. However, it can also increase the risk of a cytokine storm, which complicates disease progression. In particular, TLR3 may act by producing IFN-α and IFN-β via IRF3 within the first 24 hours post-infection (hpi), or activate the NFκB transduction pathway leading to the secretion of pro-inflammatory cytokines (IL-1α, IL-1β, IL-4 and IL-6) at 48 hpi [16]. In terms of its protective function, mice lacking TLR3 had higher viral loads and impaired lung function when infected with the mouse-adapted strain of SARS-CoV-1 (MA15) [141]. Lower levels of TLR3 expression in the peripheral blood of patients have been associated with poorer outcomes in those with severe COVID-19 [148]. Another study showed that a deficiency in the TLR3-IRF7-mediated IFN-I response is likely to result in a high mortality rates [149]. Furthermore, the TLR3 (rs3775290) polymorphism has been linked to an increased risk of pneumonia in individuals infected with SARS-CoV-2 [150]. In contrast, Chomel et al. found that neutrophils from patients with severe SARS-CoV-2 infection exhibited higher levels of TLR3 and TLR7 than those from healthy donors. Furthermore, TLR3 gene expression was found to be significantly higher in critically ill SARS-CoV-2 patients than in those with mild disease [151]. This emphasizes the complexity of TLR3's role, particularly in relation to the timing of its activation during SARS-CoV-2 infection.

3.1.3. TLR4

Computational modelling studies have suggested that TLR4 can bind directly to the S1 subunit of the SARS-CoV-2 S protein [152], as has been observed in murine and human macrophages [153]

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and NK cells [144]. This interaction triggers pro-inflammatory pathways and activates transcription factors such as NF-κB and AP-1, leading to the production of pro-inflammatory cytokines and IFNs [153–156], particularly in pDCs [157]. Crucially, TLR4 plays a dual role in COVID-19, mediating both protective and deleterious effects [158]. Although blocking TLR4 could reduce hyperinflammation in the later stages of SARS-CoV-2 infection, it could also impair IFN-I-mediated immunity in the early stages [159–163]. This highlights the importance of timing and context in TLR4-targeted treatments for COVID-19 [164]. Furthermore, the expression of TLR4 and its downstream signalling mediators, including cluster of differentiation 14 (CD14), MyD88, IRAK1 and TRIF, is significantly higher in peripheral blood mononuclear cells (PBMCs) from patients with SARS-CoV-2 infection than in healthy individuals [165,166]. Moreover, increased TLR4 activity has been observed in the myocardium of patients with severe SARS-CoV-2-induced inflammation, which is similar in severity to bacterial sepsis [167,168]. It is also noteworthy that SARS-CoV-2 utilizes the C-type lectin receptor Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN or CD209) as a co-receptor, leading to the downregulation of TLR4 function in human dendritic cells (DCs). Indeed, Van der Donk demonstrated that SARS-CoV-2 can suppress dendritic cell function via DC-SIGN-mediated Rapidly Accelerated Fibrosarcoma-1 (RAF-1) signalling following TLR4 activation. This could potentially worsen mortality in COVID-19 patients with bacterial superinfection. Blocking DC-SIGN with antibodies or inhibiting RAF-1 with a small molecule restores IFN-I and cytokine responses to lipopolysaccharide (LPS), highlighting the role of the RAF-1 pathway in TLR4 activation [169].

3.1.4. TLR7/8

An in vitro study has shown that infection of multicellular spheroids comprizing Calu-3 human lung adenocarcinoma cells and MRC-5 human lung fibroblasts with SARS-CoV-2 promotes the activation of the TLR3 and TLR7 RNA-sensing pathways. Around 48 hours after SARS-CoV-2 infection, TLR7 predominantly activates the NFκB pathway, resulting in the release of IFN-I, IFN-γ and IFN-λ3 [16]. Studies have shown that peripheral blood pDCs in humans that are deficient in TLR7 produce lower levels of IFN following SARS-CoV-2 infection. This suggests that TLR7 activity is essential for inducing IFN-I in pDCs[170,171]. Sorrentino et al. also found that IFN-λ and IFN-γ levels were dysregulated in BAL cells from patients with SARS-CoV-2 infection. They also found that patients who died from the infection had lower levels of both TLR7 and TLR8 [129]. Interestingly, Lam et al. observed an increased interaction between TLR7 and the Band 3 membrane protein on the surface of mature red blood cells (RBCs) in patients with SARS-CoV-2-associated sepsis. This interaction enhanches the ability of RBCs to bind RNA and act as scavengers [172]. TLR7 was found to be essential for mounting a robust receptor-binding domain (RBD)-specific humoral response to pathogen-like antigens (PLA)-based AP205-RBD and inactivated SARS-CoV-2 vaccines [173]. Several studies have shown that SARS-CoV-2 infection is associated with increased TLR8 mRNA expression in the nasopharyngeal epithelial cells of patients with COVID-19 compared to healthy individuals [174,175]. Additionally, patients with severe COVID-19 had significantly higher levels of both TLR7 and TLR8 gene expression than those with mild disease [176]. TLR8 is known to recognize antiphospholipid antibodies and has been found to correlate with more severe COVID-19. This suggests that it could be used as a prognostic biomarker, particularly for female patients with SARS-CoV-2 infection [176,177].

3.1.5. TLR9

It is well established that TLR9 is activated by CpG-rich unmethylated DNA motifs [178]. The presence of unmethylated CpG motifs in the genome of SARS-CoV-2 suggests the possibility of direct TLR9 activation.However, it is uncertain whether SARS-CoV-2 activates TLR9 through a direct mechanism [179]. Mitochondrial dysfunction is an indirect mechanism that has been associated with a variety of health issues [180,181] and has been observed in various viral infections [182], including SARS-CoV-2 [183,184]. The activation of TLR9 and the secretion of cytokines have been observed as

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a result of mitochondrial dysfunction (i.e. increased production of mitochondrial superoxide anions, altered mitochondrial membrane potential and enhanced mitochondrial DNA (mtDNA) release) following SARS-CoV-2 infection in human umbilical vein endothelial cells (HUVECs) [178]. Furthermore, patients infected with SARS-CoV-2 have increased levels of mtDNA in their plasma compared to uninfected patients. Impairment of mitochondrial function caused by SARS-CoV-2 infection leads to the activation of TLR9 signalling in endothelial cells, which triggers inflammatory responses and potentially contributes to the severity of COVID-19 [178]. TLR9 has also emerged as a promising therapeutic target for preventing and treating SARS-CoV-2 infection and disease. The use of TLR9 agonists as vaccine adjuvants has also been suggested[185,186]. Furthermore, elevated levels of TLR9 expression and the presence of TLR9 ligands have been identified as biomarkers for predicting a more severe outcome of SARS-CoV-2 infection [179]. Alhabibi et al. reported that certain TLR2 and TLR9 genetic variants are associated with susceptibility to and severity of COVID-19, specifically the TLR2 rs5743708 (G/A) and TLR9 rs5743836 (C/C) genotypes. These correlate with pro-inflammatory responses and COVID-19 progression.

3.2. SARS-CoV-2 Recognition by RNA Sensors

SARS-CoV-2-RNA molecules are detected by both RIG-I and MDA5 in the cytoplasm. They play a critical role in the innate immune response by promoting the expression of IFNs and other pro-inflammatory cytokines [187].

3.2.1. RIG-I

One study reported that silencing RIG-I using small interfering RNA (siRNA) in Calu-3 cells significantly decreased the expression of IFN-β expression during SARS-CoV-2 infection [188]. In line with these findings, Change et al. reported that the G protein-coupled receptor ADGRE5 (CD97) acts as a negative regulator of RIG-I by promoting its degradation and interfering with the IFN-I signalling pathway. This consequently facilitates SARS-CoV-2 replication [189]. In contrast, other studies have found that silencing the RIG-I gene does not reduce IFN-β production in Calu-3 cells infected with SARS-CoV-2 [190–192]. Nevertheless, deleting RIG-I was found to increase SARS-CoV-2 replication, suggesting that RIG-I plays a role in the antiviral defence system that is independent of the MAVS-IFN signalling pathway [192]. Furthermore, SARS-CoV-2-infected patients were found to have significantly lower levels of RIG-1 and IFN-β promoter stimulator-1 (IPS-1) than healthy individuals [193]. Taken together, these findings suggest a potential link between reduced RIG-I-mediated immune responses to SARS-CoV-2, impaired viral clearance, and fatal outcomes [193,194].

3.2.2. MDA5

Another important RLR is the MDA5 protein, which acts as the primary SARS-CoV-2 sensor in human lung cells [190,195]. Studies using both short hairpin RNA-mediated interference and CRISPR-Cas9 knockout techniques have emphasized the crucial role of MDA5 in the detection of SARS-CoV-2 RNA in Calu-3 cells [196]. The MDA5-MAVS-IRF3 pathway has been identified as essential for the induction of IFN-I/III. However, it appears to play only a minor role in the secretion of pro-inflammatory cytokines in response to SARS-CoV-2 infection [196–198]. The activity of MDA5 is enhanced by Laboratory of Genetics and Physiology 2 (LGP2), a related helicase that strengthens the IFN response by stabilizing the binding of MDA5 to short dsRNA. Despite lacking the caspase recruitment domain (CARD) necessary for initiating IFN responses, LGP2 enhances MDA5's sensitivity to viral RNA by facilitating the formation of stable filaments, thereby promoting a stronger and more sustained antiviral state [190,199,200]. Furthermore, IFN production appeared to depend critically on ISG-15-mediated ISGylation in the MDA5-mediated antiviral response [201]. Interestingly, the induction of the antiviral protein myxovirus resistance protein A (MxA) mainly occurs in uninfected bystander cells following the recognition of SARS-CoV-2 RNA by MDA5. This highlights the complex regulatory mechanisms involved [196]. Despite the robust production of IFN-

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I/III and key inflammatory mediators, such as CXCL10, TNF-α and IL-6, in response to the recognition of SARS-CoV-2 by MDA5 in both primary and immortalized lung epithelial cells, this antiviral response alone is insufficient to control SARS-CoV-2 replication [191]. Therefore, the antiviral effects resulting from the recognition of SARS-CoV-2 RNA by MDA5 seem to be limited. Effective control of SARS-CoV-2 replication requires additional immune pathways or external interventions [188,191,202]. A study by Yang et al. showed that the absence of MDA5, RIG-I or MAVS significantly increased SARS-CoV-2 replication in human epithelial cells. Wild-type (WT) cells exhibited an increase in IFN-I and III upon SARS-CoV-2 infection; however, this response was considerably diminished in MDA5-/- and MAVS-/- cells. RIG-I-/- cells maintained moderate IFN signalling; however, their ACE2 expression was found to be around 2.5 times higher than that of WT cells. These results emphasize the vital role of MDA5 in triggering the IFN-I/III response to SARS-CoV-2 and suggest that RIG-I may have an IFN-independent antiviral function [192].

3.2.3. PKR and OAS Family

The dsRNA-dependent PKR and OAS family, which are dependent on dsRNA, are integral components of the innate immune response to viral infections. Classified as ISGs, they act as dsRNA sensors [53]. Notably, PKR suppresses translation initiation by phosphorylating eukaryotic initiation factor 2 (eIF2)[203], while also acting as a signal transducer for pro-inflammatory gene expression [204]. The human OAS family consists of four IFN-regulated genes: OAS1, OAS2, OAS3 and OASL. The OAS1-3 enzymes catalyze the production of 2′-5′-linked oligoadenylates, and OASL is known for its synthase activity. These molecules activate RNase L, an endoribonuclease that breaks down single-stranded mRNA and rRNA. This process inhibits protein synthesis, thereby establishing an antiviral state [205]. The direct activation of PKR and OASL by dsRNA has been observed in respiratory epithelial cells and cardiomyocytes infected with SARS-CoV-2. Notably, a connection has been established between the OAS gene family and cardiac injury and failure in patients with severe SARS-CoV-2 infections [206]. Furthermore, recessive single-gene inborn errors in the OAS–RNase L pathway can lead to the uncontrolled production of inflammatory cytokines by mononuclear phagocytes in response to SARS-CoV-2 infection. This could contribute to the development of multisystem inflammatory syndrome (MIS-C) in children [207]. Similarly, monocytic cell lines and primary myeloid cells that are deficient in OAS1, OAS2 or RNase L produce excessive levels of inflammatory cytokines when stimulated by dsRNA or SARS-CoV-2 [207]. The N protein of SARS-CoV-2 has been observed to suppress innate immunity by binding to dsRNA via its N2b domain [208]. Notably, SARS-CoV-2 activates the PKR-mediated integrated stress response (ISR), yet subsequently prevents the formation of stress granules and the expression of ATF4/CHOP. Differences were observed between SARS-CoV-2 variants: Delta showed weaker PKR activation, whereas Omicron BA.1 exhibited increased phosphorylation of eIF2α and stress granule formation [209]. More recently, it has been demonstrated that defective RNA processing leads to impaired PKR-mediated antiviral control in brainstem neurons. Specifically, the accumulation of RNA lariats in DBR1-deficient cells disrupts stress granule formation and PKR activation mediated by G3BP. This increases susceptibility to viral infection in both in vitro and in vivo models of brainstem viral infection, including SARS-CoV-2 [210,211].

3.3. SARS-CoV-2 Recognition by Absent in Melanoma 2-Like Receptors (ALRs)

ALRs are intracellular sensors of the innate immune system that are mainly induced by IFN-I, but also by IFN-II and other proinflammatory cytokines. They belong to the PYHIN family, alongside proteins such as AIM2 and IFI16 [212].

3.3.1. IFI16/p204

IFI16, also known as p204, acts as a sensor of dsDNA viruses. It amplifies antiviral responses by inducing the transcription of RIG-I and promoting the production of interferons (IFNs) and other

 doi:10.20944/preprints202507.2587.v1

antiviral cytokines. It has recently been demonstrated that IFI16 can also sense negative-sense RNA viruses, such as the influenza virus [213]. However, the direct interaction between IFI16 and SARS-CoV-2 has not yet been elucidated. A study by Hamldar et al. found that IFI16 expression levels were significantly higher in people with confirmed SARS-CoV-2 infections than in healthy individualsA positive correlation was also observed between IFI16 expression levels and symptoms such as skeletal pain [214]. Furthermore, the upregulation of the IFI16 gene in association with IRAK4, STING, IFNAR1 and CD14 was observed in blood cells from patients with moderate-to-severe acute SARS-CoV-2 infections [215]. In this context, IFI16 could be used as a biomarker to distinguish between healthy individuals and those in the acute or post-acute phases of the COVID-19 [214].

3.3.2. AIM2

Similar to IFI16, AIM2 is a cytoplasmic sensor which recognizes the presence of dsDNA and forms an inflammasome complex known as the AIM2 inflammasome [57,216]. This complex was found to be activated in monocytes isolated from patients with COVID-19 [217]. SARS-CoV-2 genome was found in approximately 6% of blood monocytes of COVID-19 patients. Despite the infection being aborted, these cells undergo pyroptosis, which is mediated by the activation of NLRP3 and AIM2 inflammasomes, as well as by caspase-1 and gasdermin D. Furthermore, tissue-resident macrophages obtained from the lungs of patients who had undergone autopsy and had been confirmed to have SARS-CoV-2 infection have revealed the presence of activated inflammasome [217]. Consistent with this, previous studies have reported elevated levels of IL-1 cytokines in the plasma of COVID-19 patients, as well as evidence of the virus entering myeloid cells in vitro and activating the NLRP3 inflammasome and caspase-1 in blood cells [218–220].

3.4. cGAS-STING Pathway

The cGAS–STING signalling pathway has been identified as a key mediator of inflammation in several contexts, such as infection, cellular stress, tissue damage and autoimmune diseases [221]. While this pathway is primarily activated by cytosolic DNA, there is evidence to suggest that SARS-CoV-2 can activate the cGAS–STING signalling axis[222]. Studies have shown that SARS-CoV-2 proteins, including ORF9b, ORF3a and 3CL, suppress the cGAS-STING pathway, thereby promoting viral replication [147,223]. STING agonists have consistently been shown to inhibit SARS-CoV-2 infection by inducing IFN-I responses [224,225]. However, high and sustained levels of IFN-I can contribute to immunopathology during the later stages of SARS-CoV-2 infection, leading to heightened inflammation in patients and mouse models [226–229]. Moreover, Queiroz et al. found that severe cases of COVID-19 were characterized by increased expression of STING and cGAS, as well as elevated plasma levels of IFN-α, IL-6 and TNF-α, compared to non-severe cases. These factors can lead to thromboembolic events and multiple organ failure [227,229,230]. Activation of the cGAS-STING pathway in SARS-CoV-2-infected epithelial cells drives cytokine production via the NF-κB pathway. This highlights the pathway's role in cytokine responses associated with SARS-CoV-2 infection [226,231]. Studies have shown that the SARS-CoV-2 S protein promotes cell fusion and activates the cGAS–STING pathway by leaking chromatin DNA. This is evidenced by the colocalisation of cGAS with cytosolic genomic DNA in SARS-CoV-2-induced syncytia. Consequently, host self-DNA, including chromosomal and mitochondrial DNA, acts as a danger signal, triggering an IFN-mediated antiviral response [232]. Furthermore, recent studies have revealed that endothelial cells and macrophages play a pivotal role in the dysregulation of cGAS-STING responses [181]. In endothelial cells, mitochondrial dysfunction activates cGAS, leading to the expression of IFN-I and triggering cell activation and death. In macrophages, cGAS activation is triggered by DNA from phagocytosed, dying endothelial cells, primarily inducing IFN-I production [226]. In line with these findings, studies using organ-on-a-chip technology have revealed the presence of SARS-CoV-2 elements in endothelial cells. These elements have been found to be associated with mitochondrial dysfunction and the activation of the cGAS-STING signalling pathway [226].

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4. SARS-CoV-2 Evasion Strategies by PRRs

SARS-CoV-2 has evolved multiple mechanisms to evade immune recognition by PRRs at various stages. This dampens the host's IFN-mediated antiviral response, promoting replication and pathogenesis [233]. The suppression of innate immune signaling pathways also results in the weak and delayed IFN responses observed in COVID-19 patients [9,233]. The main immune evasion strategies of SARS-CoV-2 are summarized in Figure 3. One key strategy employed by SARS-CoV-2 involves modifying its RNA structure to evade recognition by RNA sensors such as RIG-I and MDA5 [234]. SARS-CoV-2, for example, uses the nsp16/nsp10 heterodimer to methylate the 5′ end of its mRNA. This mimics host mRNA, enabling the virus to evade PRRs detection and hijack the cellular translation machinery [235]. In addition, SARS-CoV-2 encodes its own capping machinery, consisting of nsp10, nsp12, nsp13, nsp14 and nsp16. This machinery further modifies the viral genome, helping SARS-CoV-2 to evade recognition by RLRs and TLRs (including TLR2, TLR3, TLR4 and TLR7) [141,236]. Accordingly, Nsp15 acts as an exoribonuclease, protecting the virus by degrading its polyuridine RNA sequences, thereby preventing immune detection and signaling activation [237,238]. Additionally, the SARS-CoV-2 M protein binds to RIG-I, MAVS and TBK1. This prevents the formation of the RIG-I–MAVS–TRAF3–TBK1 complex, thereby hindering the activation of IRF3 and the subsequent IFN response [239]. The SARS-CoV-2 N protein may bind to the DExD/H domain of RIG-I, interfering with the ATPase activity necessary for recognizing viral RNA [240]. Unexpectedly, the N protein of SARS-CoV-2 can bind tightly to DNA, thereby competing with and inhibiting the activation of cGAS [241]. Conversely, the SARS-CoV-2 3C-like protease (3CLpro) prevents the activation of RIG-I by preventing tripartite motif-containing protein 25 (TRIM25)-mediated K63-linked ubiquitination [242], while SARS-CoV-2 papain-like protease (PLpro) antagonizes the ISG15-dependent activation of MDA5 [201]. Furthermore, the SARS-CoV-2 protein ORF9b inhibits the activation of MAVS by preventing the interaction between the translocase of the outer mitochondrial membrane 70 (TOM70) protein and the heat shock protein 90 (HSP90) protein [243]. On the other hand, the Nsp5 protein impairs RIG-I signaling by cleaving its N-terminus, thereby promoting the K48-linked ubiquitination and the subsequent degradation of MAVS [244]. Additionally, the SARS-CoV-2 ORF3a protein inhibits STING activation and the nuclear accumulation of the transcription factor NF-κB [223].

High expression of the SARS-CoV-2-encoded microRNA SCV2-miR-ORF1ab-2-5p inhibits the expression of the OAS1 and OAS2 genes, as well as modulating the allelic expression of OAS1. This is associated with high susceptibility to SARS-CoV-2 infection [245]. It has finally been found that structural proteins (N, M) [240,246], and non-structural proteins (PLpro, 3CLpro, nsp12, nsp13, nsp15, nsp16) [247–252], as well as accessory proteins (ORF3b, ORF6, ORF8 and ORF9b) [147,253–255] contribute to the inhibition of IRF3 activation and its nuclear translocation. This results in the suppression of the IFN response.

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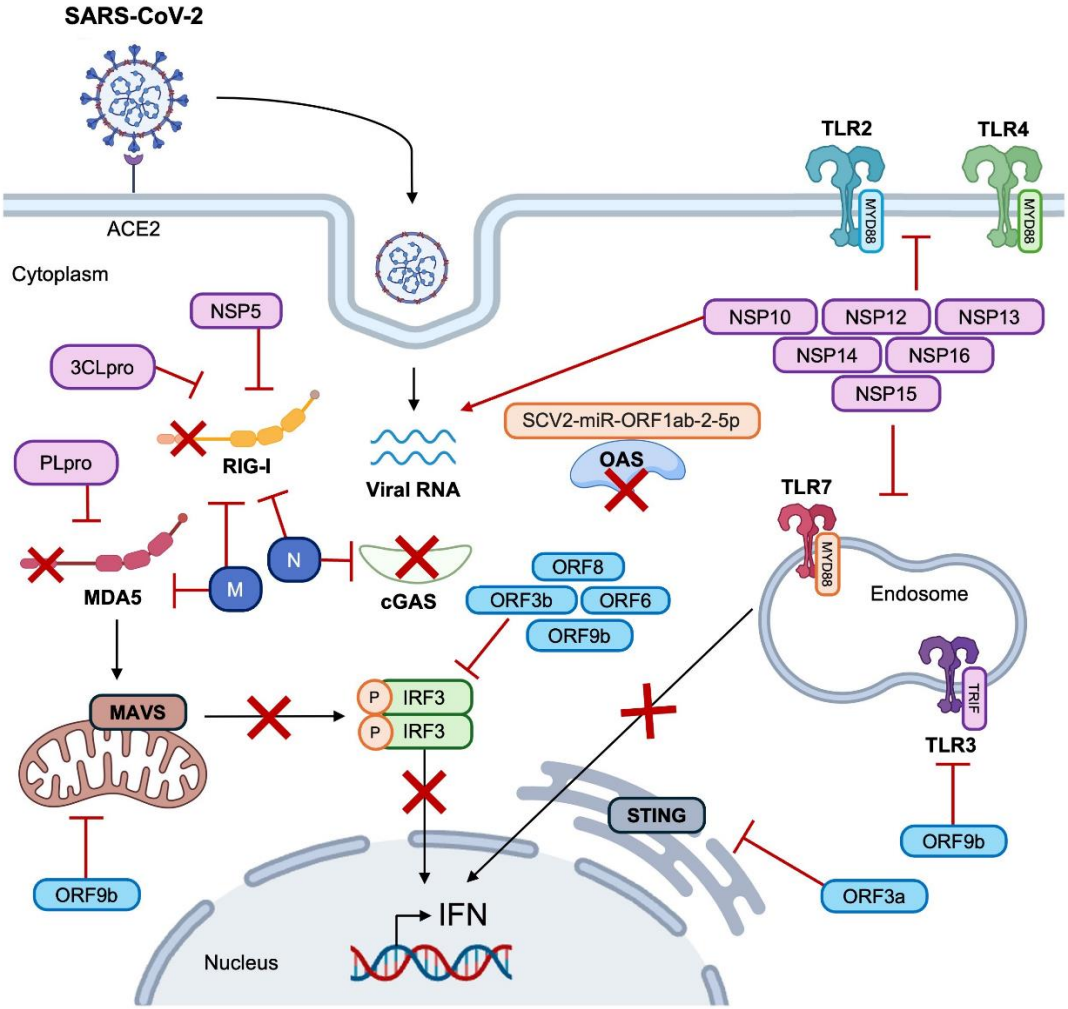

Figure 3. Strategies used by SARS-CoV-2 to evade recognition and signaling by PRRs. The figure illustrates several mechanisms that SARS-CoV-2 employs to evade immune detection by PRRs. The virus modifies its RNA, including 5′ capping by the nsp16/nsp10 complex, as well as12/13/14/15, in order to mimic host mRNA and evade detection by RNA sensors such as RIG-I and MDA5. Viral proteins, including M, N, 3CLpro and PLpro among others, interfere with key signaling molecules such as MAVS, STING and IRF3, thereby preventing the activation of IFN responses. Furthermore, accessory proteins (ORF3a/b, ORF6, ORF8, ORF9b) and viral microRNAs suppress IFN signaling pathways, collectively dampening the host's antiviral response and promoting viral replication and pathogenesis. Abbreviations: TLRs, Toll-like receptors; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated protein 5; MAVS, mitochondrial antiviral signaling; cGAS, Cyclic GMP-AMP synthase; STING, stimulator of interferon genes; OAS, 2'-5'-oligoadenylate synthetase; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; IRF3, interferon regulatory factor 3; IFN, interferon; NSP, non-structural protein; ORF, open reading frame; 3CLpro, 3C-like protease; PLpro, papain-like protease; M, membrane protein; N, nucleocapsid protein. Created with BioRender.com.

5. PRRs Agonists and Antagonists in SARS-CoV-2 Infection

Due to their critical role in innate immunity, PRRs have become a focal point of study in immunology and drug development. The variety of PRRs and the broad range of ligands they recognize make them promising therapeutic targets for diseases such as cancer, inflammation, autoimmune disorders and infections caused by pathogenic microorganisms [256]. Their versatility

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is crucial in developing innovative immunotherapeutic strategies to combat SARS-CoV-2 infection (Table 2).

5.1. TLRs Agonists and Antagonists

In particular, TLR-targeted immunotherapy can inhibit viral infection, reduce inflammation and enhance the effectiveness of vaccines against SARS-CoV-2 [257,258]. In this context, conjugating the TLR1/2 agonist Pam3CSK4 with the receptor-binding domain (RBD) in a candidate vaccine significantly enhanced antibody and cellular responses. Indeed, sera from immunized mice blocked RBD-ACE2 binding and provided protection against SARS-CoV-2 and its alpha, beta, gamma and delta variants [259]. Overexpression of TLR1/2 may exacerbate inflammation during SARS-CoV-2 infection. The TLR2 inhibitor oxPAPC has been shown to reduce both cytokine release and mortality in mice that express ACE2. This suggests that TLR2 antagonists could be an effective treatment for severe inflammation in patients with severe COVID-19 [34].

Administering synthetic dsRNA, which mimics viral nucleic acids and activates TLR3 (poly I:C), to K18-hACE2 transgenic mice during SARS-CoV-2 infection improves survival rates by reducing viral load and inflammation in lung and brain tissue [260,261]. Interestingly, the SARS-CoV-2 S protein exhibits the strongest binding affinity to TLR4 [262].

As discussed previously, the regulation of TLR4 may have a dual effect, depending on the stage of SARS-CoV-2 infection at which modulation occurs [164]. Consequently, targeting this receptor therapeutically could be a way to improve outcomes in severe cases of COVID-19. Resatorvid (also known as CLI-095 or TAK-242) is a TLR4 inhibitor that blocks the interaction between TLR4 and the proteins TIRAP and TRAM. This suppresses signaling in the TLR4/MyD88/NF-κB pathway and the activation of the NLRP3 inflammasome [263]. Conversely, stimulating PBMCs from severe COVID-19 patients, characterized by rare loss-of-function (LOF) variants of the TLR7 gene, with the TLR7 agonist imiquimod (IMQ), revealed an impaired IFN-I response. This was characterized by low levels of IRF7, IFNβ1, ISG15 and IFNγ, highlighting the importance of intact TLR7 signaling in the pathogenesis of severe COVID-19 [141]. In addition, Enpatoran, a selective inhibitor of TLR7/8 can potentially target the pro-inflammatory pathways induced by SARS-CoV-2 infection and reduce the uptake of SARS-CoV-2 RNA by RBCs [172,264]. Finally, the TLR9 agonist CpG-2722 boosts the immune response to the SARS-CoV-2 vaccine by inducing antigen-dependent T helper 1 (Th1) and Th17 responses (Table 2) [186].

5.2. RLRs Agonists and Antagonists

The modulation of RLR activity by agonists and antagonists is of considerable interest, given that these molecules have the potential to either enhance antiviral immunity or reduce excessive inflammation, particularly in the context of SARS-CoV-2 infection (Table 2) [265]. This section explores the mechanisms and applications of RLR agonists and antagonists, highlighting their significance in disease management and the development of therapies. Marx et al. demonstrated that treating a K18-hACE2 mouse model of SARS-CoV-2 infection with a RIG-1 agonist triphosphate RNA (3pRNA) protected the mice from lethal infection and promoted the development of specific neutralizing antibodies [266]. In addition, a study showed that the minimal RIG-I agonist stem-loop RNA 14 (SLR14) exhibits antiviral properties, by preventing SARS-CoV-2 infection of the lower respiratory tract and progression to severe disease through an IFN-I-dependent mechanism [267]. Furthermore, given the critical role of MDA5 in triggering antiviral immune responses within the airway epithelium [190], its agonists, such as synthetic poly(I:C) dsRNA and long viral dsRNA [268], have therapeutic potential in combatting early-stage SARS-CoV-2 infection (Table 2) [192,269].

5.3. Nucleotidyltransferase Family Agonists and Antagonists

The excessive production of inflammatory cytokines, such as IL-6, may be driven by the upregulation of NF-κB via the cGAS-STING pathway. Treatment with the STING inhibitors H-151

 doi:10.20944/preprints202507.2587.v1

and VS-X4 has been shown to effectively reduce levels of TNF and IL-6 in SARS-CoV-2-infected cells *in vitro* [231]. In contrast, the pharmacological activation of the cGAS–STING signaling pathway using the STING agonist diABZI has been shown to inhibit SARS-CoV-2 replication by stimulating the production of ISGs in transgenic mice that have been pretreated with an intranasal treatment and express human ACE2. This treatment has been shown to reduce lung inflammation and increase survival rates [224,225]. Qi et al. demonstrated that glycyrrhetinic acid (GA) mitigated SARS-CoV-2 Omicron infection in Calu-3 and MEF cells, and in mice, by binding to STING and enhancing its phosphorylation. This resulted in elevated levels of CXCL10, IFN-β, OAS1, and ISG15 mRNA [270]. These observations highlight the dual role of cGAS-STING signaling in SARS-CoV-2 infection and pathogenesis, where its hyperactivation contributes to excessive inflammation (Table 2).

Table 2. Modulation of PRRs in SARS-CoV-2 Infection: effects and therapeutic potential.

Compound	Targeted PRR	Effect of the PRR modulation	Reference
Pam3CSK4	TLR1/2	Booster of anti-RBD antibody and cellular responses in immunized mice	[259]
oxPAPC	TLR2	Reduction of cytokine and chemokine release in ACE2-expressing mice, lowering mortality compared to controls	[34]
poly IC	TLR3	Its administration to K18-hACE2 transgenic mice during SARS-CoV-2 infection improves survival by reducing viral load and inflammation in both lung and brain tissue	[260]
Resatorvid	TLR4	Suppression of TLR4/MyD88/NF-κB signaling and inhibition of NLRP3 inflammasome activation	[263]
IMQ	TLR7	IMQ stimulation on PBMC from severe COVID-19 patients with rare LOF TLR7 variant demonstrated an insufficient induction of IRF7, IFNβ1, and ISG15, as well as a reduction in IFNγ production	[141]
Enpatoran	TLR7/8	Enpatoran can reduce the uptake of SARS-CoV-2 RNA by RBCs	[172]
CpG-2722	TLR9	Booster of the immune response to SARS-CoV-2 vaccine	[186]
3pRNA	RIG-1	Improvement of survival, as evidenced by reduced viral loads in oropharyngeal swabs, lungs and brains of treated mice.	[266]
SLR14	RIG-1	Prevention of lower respiratory tract infections and severe COVID-19 disease progression through a type I IFN-dependent mechanism.	[267]
H-151 and VS-X4	cGAS-STING	Inhibits STING reducing the level of TNF and IL-6 expression in SARS-CoV-2 infected cells *in vitro*	
diABZI	cGAS–STING	Suppression of SARS-CoV-2 replication by stimulating ISGs production in transgenic mice expressing human ACE2, with a reduced lung inflammation and increased survival rates.	[225]
GA	STING	Ameliorated SARS-CoV-2 Omicron infection both inCalu-3 and in MEF cells and in mice. The transcription levels of *Cxcl10*, *Ifnβ*, *Oas1*, and *Isg15* mRNA levels in the MEF cells were up regulated.	[270]

Pam3CSK4, palmitoyl-3-cysteine-serine-lysine-4; oxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine; poly IC, polyinosinic-polycytidylic acid; IMQ, imiquimod; PBMC, peripheral blood mononuclear cells; 3pRNA, triphosphorylated RNA; SLR14, stem-loop RNA 14; diABZI, Di-cyclic amidobenzimidazole; GA, glycyrrhetinic acid.

 doi:10.20944/preprints202507.2587.v1

6. Modulation of PRRs in Long COVID

Long COVID (LC) or post-acute sequelae of SARS-CoV-2 infection (PASC) refers to a variety of symptoms that persist for weeks or months after the acute phase of a SARS-CoV-2 infection has resolved [271,272]. LC can affect individuals despite the severity of the acute infection, significantly impacting their quality of life [273]. The symptoms of LC can vary widely and may include fatigue, shortness of breath, cognitive impairment, chest pain, headaches, muscle and joint pain, insomnia, mood changes, loss of smell or taste, and heart palpitations [274]. In this scenario, the increased expression of PRRs (including TLR4, cGAS and STING) highlights their crucial role in the development and maintenance of the long-term effects of SARS-CoV-2(Table 3). Indeed, patients who experienced long-term post-COVID-19 symptoms had higher levels of cGAS, STING and IFN-α than individuals who did not experience LC symptoms [230]. Elevated levels of cGAS and STING perpetuate a systemic inflammatory state, which could lead to thromboembolic changes and multiple organ failure [226,275,276]. Cognitive impairment is another physical disorder reported in LC [277–279]. It has been demonstrated that infusing S protein into the mouse brain causes delayed cognitive deficits but the early TLR4 inhibition effectively prevents impairments to synapses and memory [280]. Furthermore, patients with mild SARS-CoV-2 infections who had the GG genotype of the TLR4-2604G>A variant exhibited increased TLR4 expression and were at a higher risk of cognitive impairment than those with the GA genotype. These results emphasize the important role of TLR4 in causing cognitive problems in humans and rodents and highlight its potential as a therapeutic target [280]. In fact, astrocytes, oligodendrocytes, endothelial cells and neurons also express TLRs, thereby contributing to neuroinflammation. This is supported by the detection of elevated levels of TLR2 and TLR4 in the brains of people who died from complications resulting from SARS-CoV-2 infection [281]. Furthermore, variations in the expression of MDA5 and OAS2 have been observed in children and adolescents with LC, compared with recovered patients without LC symptoms (matched controls, MC) and healthy controls. Age appears to play a key role in shaping the immune response to LC, with clear differences in IFN-related gene expression between children and adolescents [272]. In fact, although children typically experience mild COVID-19, some go on to develop long-term symptoms months later [282]. These observations underscore the complex interplay between innate immune sensors and the persistence of long COVID symptoms. Sustained activation of PRRs may contribute to systemic and neuroinflammatory processes, suggesting that targeting PRRs could help the manage of long-term symptoms.

Table 3. Effect of PRRs activation in long COVID.

PRR	Effect	Reference
cGAS-STING	Elevated levels lead to the onset of low-grade inflammatory diseases, including cardiomyopathy	[230]
TLR4	Increased expression is associated with cognitive deficits and synapse loss	[280]
TLR2 and TLR4	Elevated levels founded in the brains of died COVID-19 patients	[281]
OAS2 and MDA5	Differential expression between healthy controls (HC), matched controls and LC cases	[272]

cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; TLR2, Toll-like receptor 2.; TLR4, Toll-like receptor 4; OAS2, 2'-5'-oligoadenylate synthetase 2; MDA5, melanoma differentiation-associated protein 5.

7. Conclusions

Recognition of SARS-CoV-2 by PRRs leads to the activation of the IFN-dependent innate immune response. Both membrane-bound PRRs, such as TLRs, and cytosolic sensors, including MDA5, RIG-I, PKR, the OAS family, IFI16, AIM2 and cGAS–STING, detect SARS-CoV-2 components and activate downstream signaling pathways. These pathways converge on NF-κB and IRF3/7, thereby driving the production of pro-inflammatory cytokines and type I/III IFNs and establishing

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an antiviral state. It is widely acknowledged that the ability of SARS-CoV-2 to evade the host immune sensors significantly contributes to delayed or insufficient activation of the IFN response. This facilitates efficient viral replication and COVID-19 progression [283]. Conversely, SARS-CoV-2 modulates host cellular pathways to create a pro-viral environment. This leads to the abnormal activation of late-stage components of innate immunity and, consequently, harmful IFN production [284]. Notably, the activation of inflammatory pathways, such as the NLRP3 inflammasome and the cGAS-STING axis, can lead to the excessive release of cytokines [285], contributing to the cytokine storm that is a hallmark of severe cases of SARS-CoV-2 infection [231,275,286–289]. Understanding how SARS-CoV-2 interferes with these innate immune pathways could facilitate the development of new antiviral therapies, such as PRRs agonists and antagonists. Furthermore, gaining more insights into the molecular interactions between the virus and host PRRs could help to formulate more effective vaccines that elicit stronger immune responses. This could enhance protection against both existing and emerging SARS-CoV-2 variants. Considering the important role of PRRs in the development and maintenance of the long-term effects of SARS-CoV-2, fully understanding the mechanisms underlying LC symptomatology could enable better management of this complication.

Author Contributions: Conceptualization, C.S., L.M. and G.B.; data collection, L.M., G.B., M.F., C.B., A.DA., F.A., F.F., A.A., L.S.; writing—original draft preparation, L.M., G.B., M.F., C.B., A.DA..; writing—review and editing, L.M., G.B., A.P., M.B.MH. and C.S.; funding acquisition, C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by a grant to CS from University of Rome La Sapienza (Ricerca Ateneo Sapienza, Progetti medi, 2025, protocol number: RM124190A260C1F0)

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Woldemeskel, B.A.; Kwaa, A.K.; Garliss, C.C.; Laeyendecker, O.; Ray, S.C.; Blankson, J.N. Healthy Donor T Cell Responses to Common Cold Coronaviruses and SARS-CoV-2. *J. Clin. Invest.* **2020**, *130*, 6631–6638, doi:10.1172/JCI143120.
2. Ogimi, C.; Kim, Y.J.; Martin, E.T.; Huh, H.J.; Chiu, C.-H.; Englund, J.A. What's New With the Old Coronaviruses? *J. Pediatric Infect. Dis. Soc.* **2020**, *9*, 210–217, doi:10.1093/jpids/piaa037.
3. Zhang, S.; Wang, L.; Cheng, G. The Battle between Host and SARS-CoV-2: Innate Immunity and Viral Evasion Strategies. *Mol. Ther.* **2022**, *30*, 1869–1884, doi:10.1016/j.ymthe.2022.02.014.
4. Filip, R.; Gheorghita Puscaselu, R.; Anchidin-Norocel, L.; Dimian, M.; Savage, W.K. Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. *J. Pers. Med.* **2022**, *12*, doi:10.3390/jpm12081295.
5. Haldane, V.; De Foo, C.; Abdalla, S.M.; Jung, A.-S.; Tan, M.; Wu, S.; Chua, A.; Verma, M.; Shrestha, P.; Singh, S.; et al. Health Systems Resilience in Managing the COVID-19 Pandemic: Lessons from 28 Countries. *Nat. Med.* **2021**, *27*, 964–980, doi:10.1038/s41591-021-01381-y.
6. Karki, R.; Kanneganti, T.-D. Innate Immunity, Cytokine Storm, and Inflammatory Cell Death in COVID-19. *J. Transl. Med.* **2022**, *20*, 542, doi:10.1186/s12967-022-03767-z.
7. Ivashkiv, L.B.; Donlin, L.T. Regulation of Type I Interferon Responses. *Nat. Rev. Immunol.* **2014**, *14*, 36–49, doi:10.1038/nri3581.
8. Montazersaheb, S.; Hosseiniyan Khatibi, S.M.; Hejazi, M.S.; Tarhriz, V.; Farjami, A.; Ghasemian Sorbeni, F.; Farahzadi, R.; Ghasemnejad, T. COVID-19 Infection: An Overview on Cytokine Storm and Related Interventions. *Virol. J.* **2022**, *19*, 92, doi:10.1186/s12985-022-01814-1.
9. Liu, Q.; Chi, S.; Dmytruk, K.; Dmytruk, O.; Tan, S. Coronaviral Infection and Interferon Response: The Virus-Host Arms Race and COVID-19. *Viruses* **2022**, *14*, doi:10.3390/v14071349.

 doi:10.20944/preprints202507.2587.v1

10. Rabaan, A.A.; Mutair, A. Al; Aljeldah, M.; Shammari, B.R. Al; Sulaiman, T.; Alshukairi, A.N.; Alfaresi, M.; Al-Jishi, J.M.; Al Bati, N.A.; Al-Mozaini, M.A.; et al. Genetic Variants and Protective Immunity against SARS-CoV-2. *Genes (Basel).* **2022**, *13*, doi:10.3390/genes13122355.
11. Diamond, M.S.; Kanneganti, T.-D. Innate Immunity: The First Line of Defense against SARS-CoV-2. *Nat. Immunol.* **2022**, *23*, 165–176, doi:10.1038/s41590-021-01091-0.
12. van der Made, C.I.; Simons, A.; Schuurs-Hoeijmakers, J.; van den Heuvel, G.; Mantere, T.; Kersten, S.; van Deuren, R.C.; Steehouwer, M.; van Reijmersdal, S. V; Jaeger, M.; et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA* **2020**, *324*, 663–673, doi:10.1001/jama.2020.13719.
13. Asano, T.; Boisson, B.; Onodi, F.; Matuozzo, D.; Moncada-Velez, M.; Renkilaraj, M.R.L.M.; Zhang, P.; Meertens, L.; Bolze, A.; Materna, M.; et al. X-Linked Recessive TLR7 Deficiency in ~1\% of Men under 60 Years Old with Life-Threatening COVID-19. *Sci. Immunol.* **2021**, *6*, eabl4348, doi:10.1126/sciimmunol.abl4348.
14. Yamada, T.; Takaoka, A. Innate Immune Recognition against SARS-CoV-2. *Inflamm. Regen.* **2023**, *43*, 7, doi:10.1186/s41232-023-00259-5.
15. Dhangadamajhi, G.; Rout, R. Association of TLR3 Functional Variant (Rs3775291) with COVID-19 Susceptibility and Death: A Population-Scale Study. *Hum. Cell* **2021**, *34*, 1025–1027, doi:10.1007/s13577-021-00510-6.
16. Bortolotti, D.; Gentili, V.; Rizzo, S.; Schiuma, G.; Beltrami, S.; Strazzabosco, G.; Fernandez, M.; Caccuri, F.; Caruso, A.; Rizzo, R. TLR3 and TLR7 RNA Sensor Activation during SARS-CoV-2 Infection. *Microorganisms* **2021**, *9*, doi:10.3390/microorganisms9091820.
17. Poulas, K.; Farsalinos, K.; Zanidis, C. Activation of TLR7 and Innate Immunity as an Efficient Method Against COVID-19 Pandemic: Imiquimod as a Potential Therapy. *Front. Immunol.* **2020**, *11*, 1373, doi:10.3389/fimmu.2020.01373.
18. Spiering, A.E.; de Vries, T.J. Why Females Do Better: The X Chromosomal TLR7 Gene-Dose Effect in COVID-19. *Front. Immunol.* **2021**, *12*, 756262, doi:10.3389/fimmu.2021.756262.
19. Banday, A.R.; Stanifer, M.L.; Florez-Vargas, O.; Onabajo, O.O.; Papenberg, B.W.; Zahoor, M.A.; Mirabello, L.; Ring, T.J.; Lee, C.-H.; Albert, P.S.; et al. Genetic Regulation of OAS1 Nonsense-Mediated Decay Underlies Association with COVID-19 Hospitalization in Patients of European and African Ancestries. *Nat. Genet.* **2022**, *54*, 1103–1116, doi:10.1038/s41588-022-01113-z.
20. Bastard, P.; Rosen, L.B.; Zhang, Q.; Michailidis, E.; Hoffmann, H.-H.; Zhang, Y.; Dorgham, K.; Philippot, Q.; Rosain, J.; Béziat, V.; et al. Autoantibodies against Type I IFNs in Patients with Life-Threatening COVID-19. *Science (80-.).* **2020**, *370*, eabd4585, doi:10.1126/science.abd4585.
21. Frasca, F.; Scordio, M.; Santinelli, L.; Gabriele, L.; Gandini, O.; Criniti, A.; Pierangeli, A.; Angeloni, A.; Mastroianni, C.M.; d'Ettorre, G.; et al. Anti-IFN-α/-ω Neutralizing Antibodies from COVID-19 Patients Correlate with Downregulation of IFN Response and Laboratory Biomarkers of Disease Severity. *Eur. J. Immunol.* **2022**, *52*, 1120–1128, doi:https://doi.org/10.1002/eji.202249824.
22. Scordio, M.; Frasca, F.; Santinelli, L.; Sorrentino, L.; Pierangeli, A.; Turriziani, O.; Mastroianni, C.M.; Antonelli, G.; Viscidi, R.P.; d'Ettorre, G.; et al. High Frequency of Neutralizing Antibodies to Type I Interferon in HIV-1 Patients Hospitalized for COVID-19. *Clin. Immunol.* **2022**, *241*, 109068, doi:https://doi.org/10.1016/j.clim.2022.109068.
23. Zhang, Q.; Pizzorno, A.; Miorin, L.; Bastard, P.; Gervais, A.; Le Voyer, T.; Bizien, L.; Manry, J.; Rosain, J.; Philippot, Q.; et al. Autoantibodies against Type I IFNs in Patients with Critical Influenza Pneumonia. *J. Exp. Med.* **2022**, *219*, e20220514, doi:10.1084/jem.20220514.
24. Isazadeh, A.; Heris, J.A.; Shahabi, P.; Mohammadinasab, R.; Shomali, N.; Nasiri, H.; Valedkarimi, Z.;

 doi:10.20944/preprints202507.2587.v1

Khosroshahi, A.J.; Hajazimian, S.; Akbari, M.; et al. Pattern-Recognition Receptors (PRRs) in SARS-CoV-2. *Life Sci.* **2023**, *329*, 121940, doi:https://doi.org/10.1016/j.lfs.2023.121940.

25. Florindo, H.F.; Kleiner, R.; Vaskovich-Koubi, D.; Acúrcio, R.C.; Carreira, B.; Yeini, E.; Tiram, G.; Liubomirski, Y.; Satchi-Fainaro, R. Immune-Mediated Approaches against COVID-19. *Nat. Nanotechnol.* **2020**, *15*, 630–645, doi:10.1038/s41565-020-0732-3.
26. Gewaid, H.; Bowie, A.G. Regulation of Type I and Type III Interferon Induction in Response to Pathogen Sensing. *Curr. Opin. Immunol.* **2024**, *87*, 102424, doi:https://doi.org/10.1016/j.coi.2024.102424.
27. Lee, H.-R.; Choi, U.Y.; Hwang, S.-W.; Kim, S.; Jung, J.U. Viral Inhibition of PRR-Mediated Innate Immune Response: Learning from KSHV Evasion Strategies. *Mol. Cells* **2016**, *39*, 777–782, doi:https://doi.org/10.14348/molcells.2016.0232.
28. Ma, M.; Jiang, W.; Zhou, R. DAMPs and DAMP-Sensing Receptors in Inflammation and Diseases. *Immunity* **2024**, *57*, 752–771, doi:https://doi.org/10.1016/j.immuni.2024.03.002.
29. Takeuchi, O.; Akira, S. Innate Immunity to Virus Infection. *Immunol. Rev.* **2009**, *227*, 75–86, doi:10.1111/j.1600-065X.2008.00737.x.
30. Carty, M.; Bowie, A.G. Recent Insights into the Role of Toll-like Receptors in Viral Infection. *Clin. Exp. Immunol.* **2010**, *161*, 397–406, doi:10.1111/j.1365-2249.2010.04196.x.
31. Sabroe, I.; Read, R.C.; Whyte, M.K.B.; Dockrell, D.H.; Vogel, S.N.; Dower, S.K. Toll-like Receptors in Health and Disease: Complex Questions Remain. *J. Immunol.* **2003**, *171*, 1630–1635, doi:10.4049/jimmunol.171.4.1630.
32. Liu, Y.; Yin, H.; Zhao, M.; Lu, Q. TLR2 and TLR4 in Autoimmune Diseases: A Comprehensive Review. *Clin. Rev. Allergy Immunol.* **2014**, *47*, 136–147, doi:10.1007/s12016-013-8402-y.
33. Watters, T.M.; Kenny, E.F.; O'Neill, L.A.J. Structure, Function and Regulation of the Toll/IL-1 Receptor Adaptor Proteins. *Immunol. Cell Biol.* **2007**, *85*, 411–419, doi:https://doi.org/10.1038/sj.icb.7100095.
34. Zheng, M.; Karki, R.; Williams, E.P.; Yang, D.; Fitzpatrick, E.; Vogel, P.; Jonsson, C.B.; Kanneganti, T.-D. TLR2 Senses the SARS-CoV-2 Envelope Protein to Produce Inflammatory Cytokines. *Nat. Immunol.* **2021**, *22*, 829–838, doi:10.1038/s41590-021-00937-x.
35. Yamamoto, M.; Sato, S.; Hemmi, H.; Hoshino, K.; Kaisho, T.; Sanjo, H.; Takeuchi, O.; Sugiyama, M.; Okabe, M.; Takeda, K.; et al. Role of Adaptor TRIF in the MyD88-Independent Toll-Like Receptor Signaling Pathway. *Science (80-.).* **2003**, *301*, 640–643, doi:10.1126/science.1087262.
36. Kurt-Jones, E.A.; Popova, L.; Kwinn, L.; Haynes, L.M.; Jones, L.P.; Tripp, R.A.; Walsh, E.E.; Freeman, M.W.; Golenbock, D.T.; Anderson, L.J.; et al. Pattern Recognition Receptors TLR4 and CD14 Mediate Response to Respiratory Syncytial Virus. *Nat. Immunol.* **2000**, *1*, 398–401, doi:10.1038/80833.
37. Kawai, T.; Akira, S. Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity. *Immunity* **2011**, *34*, 637–650, doi:https://doi.org/10.1016/j.immuni.2011.05.006.
38. Richez, C.; Blanco, P.; Rifkin, I.; Moreau, J.-F.; Schaeverbeke, T. Role for Toll-like Receptors in Autoimmune Disease: The Example of Systemic Lupus Erythematosus. *Jt. Bone Spine* **2011**, *78*, 124–130, doi:https://doi.org/10.1016/j.jbspin.2010.09.005.
39. Chen, J.; Ng, M.M.-L.; Chu, J.J.H. Activation of TLR2 and TLR6 by Dengue NS1 Protein and Its Implications in the Immunopathogenesis of Dengue Virus Infection. *PLOS Pathog.* **2015**, *11*, e1005053.
40. R., M.M.; N., B.G.; M., C.A.; J., A.L.; M., H.L.; A., T.R.; A., K.-J.E.; W., F.R. Respiratory Syncytial Virus Activates Innate Immunity through Toll-Like Receptor 2 . *J. Virol.* **2009**, *83*, 1492–1500, doi:10.1128/jvi.00671-08.
41. Nakao, Y.; Funami, K.; Kikkawa, S.; Taniguchi, M.; Nishiguchi, M.; Fukumori, Y.; Seya, T.; Matsumoto, M. Surface-Expressed TLR6 Participates in the Recognition of Diacylated Lipopeptide and Peptidoglycan in

 doi:10.20944/preprints202507.2587.v1

Human Cells. *J. Immunol.* **2005**, *174*, 1566–1573, doi:10.4049/jimmunol.174.3.1566.

42. Diebold, S.S.; Kaisho, T.; Hemmi, H.; Akira, S.; Reis e Sousa, C. Innate Antiviral Responses by Means of TLR7-Mediated Recognition of Single-Stranded RNA. *Science (80-.).* **2004**, *303*, 1529–1531, doi:10.1126/science.1093616.
43. Ferrao, R.; Zhou, H.; Shan, Y.; Liu, Q.; Li, Q.; Shaw, D.E.; Li, X.; Wu, H. IRAK4 Dimerization and Trans-Autophosphorylation Are Induced by Myddosome Assembly. *Mol. Cell* **2014**, *55*, 891–903, doi:https://doi.org/10.1016/j.molcel.2014.08.006.
44. Cushing, L.; Stochaj, W.; Siegel, M.; Czerwinski, R.; Dower, K.; Wright, Q.; Hirschfield, M.; Casanova, J.-L.; Picard, C.; Puel, A.; et al. Interleukin 1/Toll-like Receptor-Induced Autophosphorylation Activates Interleukin 1 Receptor-Associated Kinase 4 and Controls Cytokine Induction in a Cell Type-Specific Manner. *J. Biol. Chem.* **2014**, *289*, 10865–10875, doi:https://doi.org/10.1074/jbc.M113.544809.
45. Brikos, C.; Wait, R.; Begum, S.; O'Neill, L.A.J.; Saklatvala, J. Mass Spectrometric Analysis of the Endogenous Type I Interleukin-1 (IL-1) Receptor Signaling Complex Formed after IL-1 Binding Identifies IL-1RAcP, MyD88, and IRAK-4 as the Stable Components*. *Mol. Cell. Proteomics* **2007**, *6*, 1551–1559, doi:https://doi.org/10.1074/mcp.M600455-MCP200.
46. Hemmi, H.; Takeuchi, O.; Kawai, T.; Kaisho, T.; Sato, S.; Sanjo, H.; Matsumoto, M.; Hoshino, K.; Wagner, H.; Takeda, K.; et al. A Toll-like Receptor Recognizes Bacterial DNA. *Nature* **2000**, *408*, 740–745, doi:10.1038/35047123.
47. Kikkert, M. Innate Immune Evasion by Human Respiratory RNA Viruses. *J. Innate Immun.* **2019**, *12*, 4–20, doi:10.1159/000503030.
48. Fensterl, V.; Chattopadhyay, S.; Sen, G.C. No Love Lost Between Viruses and Interferons. *Annu. Rev. Virol.* **2015**, *2*, 549–572, doi:https://doi.org/10.1146/annurev-virology-100114-055249.
49. Cheng, G.; Zhong, J.; Chung, J.; Chisari, F. V Double-Stranded DNA and Double-Stranded RNA Induce a Common Antiviral Signaling Pathway in Human Cells. *Proc. Natl. Acad. Sci.* **2007**, *104*, 9035–9040, doi:10.1073/pnas.0703285104.
50. Kyung-Soo, I.; Sun-Hwa, L.; Y., R.J.; Lai-Yee, W.; Zsolt, T.; Keigo, M.; James, O.J.-H.; U., J.J. Inhibition of RIG-I-Mediated Signaling by Kaposi's Sarcoma-Associated Herpesvirus-Encoded Deubiquitinase ORF64. *J. Virol.* **2011**, *85*, 10899–10904, doi:10.1128/jvi.00690-11.
51. Pichlmair, A.; Schulz, O.; Tan, C.P.; Näslund, T.I.; Liljeström, P.; Weber, F.; Reis e Sousa, C. RIG-I-Mediated Antiviral Responses to Single-Stranded RNA Bearing 5'-Phosphates. *Science (80-.).* **2006**, *314*, 997–1001, doi:10.1126/science.1132998.
52. Brisse, M.; Ly, H. Comparative Structure and Function Analysis of the RIG-I-Like Receptors: RIG-I and MDA5. *Front. Immunol.* **2019**, *10*, 1586, doi:10.3389/fimmu.2019.01586.
53. Hovanessian, A.G. On the Discovery of Interferon-Inducible, Double-Stranded RNA Activated Enzymes: The 2'-5'oligoadenylate Synthetases and the Protein Kinase PKR. *Cytokine Growth Factor Rev.* **2007**, *18*, 351–361, doi:10.1016/j.cytogfr.2007.06.003.
54. Schwartz, S.L.; Conn, G.L. RNA Regulation of the Antiviral Protein 2'-5'-Oligoadenylate Synthetase. *Wiley Interdiscip. Rev. RNA* **2019**, *10*, e1534, doi:10.1002/wrna.1534.
55. Yang, K.; Dong, B.; Asthana, A.; Silverman, R.H.; Yan, N. RNA Helicase SKIV2L Limits Antiviral Defense and Autoinflammation Elicited by the OAS-RNase L Pathway. *EMBO J.* **2024**, *43*, 3876–3894, doi:10.1038/s44318-024-00187-1.
56. McAllister, C.S.; Taghavi, N.; Samuel, C.E. Protein Kinase PKR Amplification of Interferon β Induction Occurs through Initiation Factor EIF-2α-Mediated Translational Control. *J. Biol. Chem.* **2012**, *287*, 36384–36392, doi:10.1074/jbc.M112.390039.

 doi:10.20944/preprints202507.2587.v1

57. Hornung, V.; Ablasser, A.; Charrel-Dennis, M.; Bauernfeind, F.; Horvath, G.; Caffrey, D.R.; Latz, E.; Fitzgerald, K.A. AIM2 Recognizes Cytosolic DsDNA and Forms a Caspase-1-Activating Inflammasome with ASC. *Nature* **2009**, *458*, 514–518, doi:10.1038/nature07725.
58. Mogensen, T.H.; Paludan, S.R. Reading the Viral Signature by Toll-like Receptors and Other Pattern Recognition Receptors. *J. Mol. Med. (Berl).* **2005**, *83*, 180–192, doi:10.1007/s00109-004-0620-6.
59. Kumari, P.; Russo, A.J.; Shivcharan, S.; Rathinam, V.A. AIM2 in Health and Disease: Inflammasome and Beyond. *Immunol. Rev.* **2020**, *297*, 83–95, doi:10.1111/imr.12903.
60. Liu, J.; Zhou, J.; Luan, Y.; Li, X.; Meng, X.; Liao, W.; Tang, J.; Wang, Z. CGAS-STING, Inflammasomes and Pyroptosis: An Overview of Crosstalk Mechanism of Activation and Regulation. *Cell Commun. Signal.* **2024**, *22*, 22, doi:10.1186/s12964-023-01466-w.
61. Gray, E.E.; Winship, D.; Snyder, J.M.; Child, S.J.; Geballe, A.P.; Stetson, D.B. The AIM2-like Receptors Are Dispensable for the Interferon Response to Intracellular DNA. *Immunity* **2016**, *45*, 255–266, doi:10.1016/j.immuni.2016.06.015.
62. Liu, S.; Grinberg, I.; Rappe, A.M. Intrinsic Ferroelectric Switching from First Principles. *Nature* **2016**, *534*, 360–363, doi:10.1038/nature18286.
63. Ma, Z.; Jacobs, S.R.; West, J.A.; Stopford, C.; Zhang, Z.; Davis, Z.; Barber, G.N.; Glaunsinger, B.A.; Dittmer, D.P.; Damania, B. Modulation of the CGAS-STING DNA Sensing Pathway by Gammaherpesviruses. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, E4306-15, doi:10.1073/pnas.1503831112.
64. Ablasser, A.; Goldeck, M.; Cavlar, T.; Deimling, T.; Witte, G.; Röhl, I.; Hopfner, K.-P.; Ludwig, J.; Hornung, V. CGAS Produces a 2′-5′-Linked Cyclic Dinucleotide Second Messenger That Activates STING. *Nature* **2013**, *498*, 380–384, doi:10.1038/nature12306.
65. Chen, C.; Xu, P. Cellular Functions of CGAS-STING Signaling. *Trends Cell Biol.* **2023**, *33*, 630–648, doi:10.1016/j.tcb.2022.11.001.
66. Zhou, J.; Zhuang, Z.; Li, J.; Feng, Z. Significance of the CGAS-STING Pathway in Health and Disease. *Int. J. Mol. Sci.* **2023**, *24*, doi:10.3390/ijms241713316.
67. Sun, L.; Wu, J.; Du, F.; Chen, X.; Chen, Z.J. Cyclic GMP-AMP Synthase Is a Cytosolic DNA Sensor That Activates the Type I Interferon Pathway. *Science* **2013**, *339*, 786–791, doi:10.1126/science.1232458.
68. Dunphy, G.; Flannery, S.M.; Almine, J.F.; Connolly, D.J.; Paulus, C.; Jønsson, K.L.; Jakobsen, M.R.; Nevels, M.M.; Bowie, A.G.; Unterholzner, L. Non-Canonical Activation of the DNA Sensing Adaptor STING by ATM and IFI16 Mediates NF-KB Signaling after Nuclear DNA Damage. *Mol. Cell* **2018**, *71*, 745-760.e5, doi:10.1016/j.molcel.2018.07.034.
69. Berthelot, J.-M.; Drouet, L.; Lioté, F. Kawasaki-like Diseases and Thrombotic Coagulopathy in COVID-19: Delayed over-Activation of the STING Pathway? *Emerg. Microbes Infect.* **2020**, *9*, 1514–1522, doi:10.1080/22221751.2020.1785336.
70. Berthelot, J.-M.; Lioté, F. COVID-19 as a STING Disorder with Delayed over-Secretion of Interferon-Beta. *EBioMedicine* **2020**, *56*, 102801, doi:10.1016/j.ebiom.2020.102801.
71. ISAACS, A.; LINDENMANN, J. Virus Interference. I. The Interferon. *Proc. R. Soc. London. Ser. B, Biol. Sci.* **1957**, *147*, 258–267, doi:10.1098/rspb.1957.0048.
72. Le Page, C.; Génin, P.; Baines, M.G.; Hiscott, J. Interferon Activation and Innate Immunity. *Rev. Immunogenet.* **2000**, *2*, 374–386.
73. McNab, F.; Mayer-Barber, K.; Sher, A.; Wack, A.; O'Garra, A. Type I Interferons in Infectious Disease. *Nat. Rev. Immunol.* **2015**, *15*, 87–103, doi:10.1038/nri3787.
74. Rusinova, I.; Forster, S.; Yu, S.; Kannan, A.; Masse, M.; Cumming, H.; Chapman, R.; Hertzog, P.J. Interferome v2.0: An Updated Database of Annotated Interferon-Regulated Genes. *Nucleic Acids Res.* **2013**,

 doi:10.20944/preprints202507.2587.v1

41, D1040-6, doi:10.1093/nar/gks1215.

75. Rong, L.; Perelson, A.S. Treatment of Hepatitis C Virus Infection with Interferon and Small Molecule Direct Antivirals: Viral Kinetics and Modeling. *Crit. Rev. Immunol.* **2010**, *30*, 131–148, doi:10.1615/critrevimmunol.v30.i2.30.
76. Tsubota, A.; Fujise, K.; Namiki, Y.; Tada, N. Peginterferon and Ribavirin Treatment for Hepatitis C Virus Infection. *World J. Gastroenterol.* **2011**, *17*, 419–432, doi:10.3748/wjg.v17.i4.419.
77. Rizza, P.; Moretti, F.; Belardelli, F. Recent Advances on the Immunomodulatory Effects of IFN-Alpha: Implications for Cancer Immunotherapy and Autoimmunity. *Autoimmunity* **2010**, *43*, 204–209, doi:10.3109/08916930903510880.
78. Kotredes, K.P.; Gamero, A.M. Interferons as Inducers of Apoptosis in Malignant Cells. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2013**, *33*, 162–170, doi:10.1089/jir.2012.0110.
79. Antonelli, G.; Scagnolari, C.; Moschella, F.; Proietti, E. Twenty-Five Years of Type I Interferon-Based Treatment: A Critical Analysis of Its Therapeutic Use. *Cytokine Growth Factor Rev.* **2015**, *26*, 121–131, doi:10.1016/j.cytogfr.2014.12.006.
80. Chelbi-Alix, M.K.; Wietzerbin, J. Interferon, a Growing Cytokine Family: 50 Years of Interferon Research. *Biochimie* **2007**, *89*, 713–718, doi:10.1016/j.biochi.2007.05.001.
81. Channappanavar, R.; Fehr, A.R.; Vijay, R.; Mack, M.; Zhao, J.; Meyerholz, D.K.; Perlman, S. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe* **2016**, *19*, 181–193, doi:10.1016/j.chom.2016.01.007.
82. Hertzog, P.; Forster, S.; Samarajiwa, S. Systems Biology of Interferon Responses. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2011**, *31*, 5–11, doi:10.1089/jir.2010.0126.
83. Pestka, S.; Krause, C.D.; Walter, M.R. Interferons, Interferon-like Cytokines, and Their Receptors. *Immunol. Rev.* **2004**, *202*, 8–32, doi:10.1111/j.0105-2896.2004.00204.x.
84. De Andrea, M.; Ravera, R.; Gioia, D.; Gariglio, M.; Landolfo, S. The Interferon System: An Overview. *Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc.* **2002**, *6 Suppl A*, A41-6; discussion A55-8, doi:10.1053/ejpn.2002.0573.
85. Borden, E.C.; Sen, G.C.; Uze, G.; Silverman, R.H.; Ransohoff, R.M.; Foster, G.R.; Stark, G.R. Interferons at Age 50: Past, Current and Future Impact on Biomedicine. *Nat. Rev. Drug Discov.* **2007**, *6*, 975–990, doi:10.1038/nrd2422.
86. Scagnolari, C.; Antonelli, G. Type I Interferon and HIV: Subtle Balance between Antiviral Activity, Immunopathogenesis and the Microbiome. *Cytokine Growth Factor Rev.* **2018**, *40*, 19–31, doi:10.1016/j.cytogfr.2018.03.003.
87. Kalliolias, G.D.; Ivashkiv, L.B. Overview of the Biology of Type I Interferons. *Arthritis Res. Ther.* 2010, *12 Suppl 1*, S1.
88. Fensterl, V.; Sen, G.C. Interferons and Viral Infections. *Biofactors* **2009**, *35*, 14–20, doi:10.1002/biof.6.
89. Wells, A.I.; Coyne, C.B. Type III Interferons in Antiviral Defenses at Barrier Surfaces. *Trends Immunol.* **2018**, *39*, 848–858, doi:10.1016/j.it.2018.08.008.
90. de Weerd, N.A.; Nguyen, T. The Interferons and Their Receptors--Distribution and Regulation. *Immunol. Cell Biol.* **2012**, *90*, 483–491, doi:10.1038/icb.2012.9.
91. Shaw, A.E.; Hughes, J.; Gu, Q.; Behdenna, A.; Singer, J.B.; Dennis, T.; Orton, R.J.; Varela, M.; Gifford, R.J.; Wilson, S.J.; et al. Fundamental Properties of the Mammalian Innate Immune System Revealed by Multispecies Comparison of Type I Interferon Responses. *PLoS Biol.* **2017**, *15*, e2004086, doi:10.1371/journal.pbio.2004086.
92. Li, S.-F.; Gong, M.-J.; Zhao, F.-R.; Shao, J.-J.; Xie, Y.-L.; Zhang, Y.-G.; Chang, H.-Y. Type I Interferons:

 doi:10.20944/preprints202507.2587.v1

Distinct Biological Activities and Current Applications for Viral Infection. *Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* **2018**, *51*, 2377–2396, doi:10.1159/000495897.

93. Chin, K.L.; Anis, F.Z.; Sarmiento, M.E.; Norazmi, M.N.; Acosta, A. Role of Interferons in the Development of Diagnostics, Vaccines, and Therapy for Tuberculosis. *J. Immunol. Res.* **2017**, *2017*, 5212910, doi:10.1155/2017/5212910.
94. Perry, A.K.; Chen, G.; Zheng, D.; Tang, H.; Cheng, G. The Host Type I Interferon Response to Viral and Bacterial Infections. *Cell Res.* **2005**, *15*, 407–422, doi:10.1038/sj.cr.7290309.
95. Levy, D.E.; Marié, I.J.; Durbin, J.E. Induction and Function of Type I and III Interferon in Response to Viral Infection. *Curr. Opin. Virol.* **2011**, *1*, 476–486, doi:10.1016/j.coviro.2011.11.001.
96. Piehler, J.; Thomas, C.; Garcia, K.C.; Schreiber, G. Structural and Dynamic Determinants of Type I Interferon Receptor Assembly and Their Functional Interpretation. *Immunol. Rev.* **2012**, *250*, 317–334, doi:10.1111/imr.12001.
97. Ye, J.; Ortaldo, J.R.; Conlon, K.; Winkler-Pickett, R.; Young, H.A. Cellular and Molecular Mechanisms of IFN-Gamma Production Induced by IL-2 and IL-12 in a Human NK Cell Line. *J. Leukoc. Biol.* **1995**, *58*, 225–233, doi:10.1002/jlb.58.2.225.
98. Chai, H.; Gu, Q.; Robertson, D.L.; Hughes, J. Defining the Characteristics of Interferon-Alpha-Stimulated Human Genes: Insight from Expression Data and Machine Learning. *Gigascience* **2022**, *11*, doi:10.1093/gigascience/giac103.
99. Takaoka, A.; Yanai, H. Interferon Signalling Network in Innate Defence. *Cell. Microbiol.* **2006**, *8*, 907–922, doi:10.1111/j.1462-5822.2006.00716.x.
100. Kak, G.; Raza, M.; Tiwari, B.K. Interferon-Gamma (IFN-γ): Exploring Its Implications in Infectious Diseases. *Biomol. Concepts* **2018**, *9*, 64–79, doi:10.1515/bmc-2018-0007.
101. Manivasagam, S.; Klein, R.S. Type III Interferons: Emerging Roles in Autoimmunity. *Front. Immunol.* **2021**, *12*, 764062, doi:10.3389/fimmu.2021.764062.
102. Kotenko, S. V; Durbin, J.E. Contribution of Type III Interferons to Antiviral Immunity: Location, Location, Location. *J. Biol. Chem.* **2017**, *292*, 7295–7303, doi:10.1074/jbc.R117.777102.
103. Lazear, H.M.; Schoggins, J.W.; Diamond, M.S. Shared and Distinct Functions of Type I and Type III Interferons. *Immunity* **2019**, *50*, 907–923, doi:10.1016/j.immuni.2019.03.025.
104. Langer, J.A. Type I Interferons BT - Encyclopedia of Signaling Molecules. In; Choi, S., Ed.; Springer International Publishing: Cham, 2018; pp. 5787–5794 ISBN 978-3-319-67199-4.
105. Haque, S.J.; Williams, B.R. Signal Transduction in the Interferon System. *Semin. Oncol.* **1998**, *25*, 14–22.
106. Li, M.M.H.; MacDonald, M.R.; Rice, C.M. To Translate, or Not to Translate: Viral and Host MRNA Regulation by Interferon-Stimulated Genes. *Trends Cell Biol.* **2015**, *25*, 320–329, doi:10.1016/j.tcb.2015.02.001.
107. Stanton, G.J.; Weigent, D.A.; Fleischmann, W.R.J.; Dianzani, F.; Baron, S. Interferon Review. *Invest. Radiol.* **1987**, *22*, 259–273, doi:10.1097/00004424-198703000-00017.
108. Kalvakolanu, D. V; Borden, E.C. An Overview of the Interferon System: Signal Transduction and Mechanisms of Action. *Cancer Invest.* **1996**, *14*, 25–53, doi:10.3109/07357909609018435.
109. Baum, A.; García-Sastre, A. Induction of Type I Interferon by RNA Viruses: Cellular Receptors and Their Substrates. *Amino Acids* **2010**, *38*, 1283–1299, doi:10.1007/s00726-009-0374-0.
110. Lee, J.-H.; Koepke, L.; Kirchhoff, F.; Sparrer, K.M.J. Interferon Antagonists Encoded by SARS-CoV-2 at a Glance. *Med. Microbiol. Immunol.* **2023**, *212*, 125–131, doi:10.1007/s00430-022-00734-9.
111. Kotenko, S. V; Rivera, A.; Parker, D.; Durbin, J.E. Type III IFNs: Beyond Antiviral Protection. *Semin. Immunol.* **2019**, *43*, 101303, doi:10.1016/j.smim.2019.101303.

 doi:10.20944/preprints202507.2587.v1

112. Odendall, C.; Dixit, E.; Stavru, F.; Bierne, H.; Franz, K.M.; Durbin, A.F.; Boulant, S.; Gehrke, L.; Cossart, P.; Kagan, J.C. Diverse Intracellular Pathogens Activate Type III Interferon Expression from Peroxisomes. *Nat. Immunol.* **2014**, *15*, 717–726, doi:10.1038/ni.2915.
113. Voigt, E.A.; Yin, J. Kinetic Differences and Synergistic Antiviral Effects Between Type I and Type III Interferon Signaling Indicate Pathway Independence. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2015**, *35*, 734–747, doi:10.1089/jir.2015.0008.
114. Jilg, N.; Lin, W.; Hong, J.; Schaefer, E.A.; Wolski, D.; Meixong, J.; Goto, K.; Brisac, C.; Chusri, P.; Fusco, D.N.; et al. Kinetic Differences in the Induction of Interferon Stimulated Genes by Interferon-α and Interleukin 28B Are Altered by Infection with Hepatitis C Virus. *Hepatology* **2014**, *59*, 1250–1261, doi:10.1002/hep.26653.
115. Kohli, A.; Zhang, X.; Yang, J.; Russell, R.S.; Donnelly, R.P.; Sheikh, F.; Sherman, A.; Young, H.; Imamichi, T.; Lempicki, R.A.; et al. Distinct and Overlapping Genomic Profiles and Antiviral Effects of Interferon-λ and -α on HCV-Infected and Noninfected Hepatoma Cells. *J. Viral Hepat.* **2012**, *19*, 843–853, doi:https://doi.org/10.1111/j.1365-2893.2012.01610.x.
116. Bolen, C.R.; Ding, S.; Robek, M.D.; Kleinstein, S.H. Dynamic Expression Profiling of Type I and Type III Interferon-Stimulated Hepatocytes Reveals a Stable Hierarchy of Gene Expression. *Hepatology* **2014**, *59*, 1262–1272, doi:10.1002/hep.26657.
117. Zhang, X.; Bogunovic, D.; Payelle-Brogard, B.; Francois-Newton, V.; Speer, S.D.; Yuan, C.; Volpi, S.; Li, Z.; Sanal, O.; Mansouri, D.; et al. Human Intracellular ISG15 Prevents Interferon-α/β over-Amplification and Auto-Inflammation. *Nature* **2015**, *517*, 89–93, doi:10.1038/nature13801.
118. François-Newton, V.; Magno de Freitas Almeida, G.; Payelle-Brogard, B.; Monneron, D.; Pichard-Garcia, L.; Piehler, J.; Pellegrini, S.; Uzé, G. USP18-Based Negative Feedback Control Is Induced by Type I and Type III Interferons and Specifically Inactivates Interferon α Response. *PLoS One* **2011**, *6*, e22200, doi:10.1371/journal.pone.0022200.
119. Walker, F.C.; Sridhar, P.R.; Baldridge, M.T. Differential Roles of Interferons in Innate Responses to Mucosal Viral Infections. *Trends Immunol.* **2021**, *42*, 1009–1023, doi:10.1016/j.it.2021.09.003.
120. Zhou, J.-H.; Wang, Y.-N.; Chang, Q.-Y.; Ma, P.; Hu, Y.; Cao, X. Type III Interferons in Viral Infection and Antiviral Immunity. *Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* **2018**, *51*, 173–185, doi:10.1159/000495172.
121. Scagnolari, C.; Monteleone, K.; Selvaggi, C.; Pierangeli, A.; D'Ettorre, G.; Mezzaroma, I.; Turriziani, O.; Gentile, M.; Vullo, V.; Antonelli, G. ISG15 Expression Correlates with HIV-1 Viral Load and with Factors Regulating T Cell Response. *Immunobiology* **2016**, *221*, 282–290, doi:10.1016/j.imbio.2015.10.007.
122. Cheriyath, V.; Leaman, D.W.; Borden, E.C. Emerging Roles of FAM14 Family Members (G1P3/ISG 6-16 and ISG12/IFI27) in Innate Immunity and Cancer. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2011**, *31*, 173–181, doi:10.1089/jir.2010.0105.
123. Boasso, A. Type I Interferon at the Interface of Antiviral Immunity and Immune Regulation: The Curious Case of HIV-1. *Scientifica (Cairo).* **2013**, *2013*, 580968, doi:10.1155/2013/580968.
124. Brulois, K.; Jung, J.U. Interplay between Kaposi's Sarcoma-Associated Herpesvirus and the Innate Immune System. *Cytokine Growth Factor Rev.* **2014**, *25*, 597–609, doi:10.1016/j.cytogfr.2014.06.001.
125. Schneider, W.M.; Chevillotte, M.D.; Rice, C.M. Interferon-Stimulated Genes: A Complex Web of Host Defenses. *Annu. Rev. Immunol.* **2014**, *32*, 513–545, doi:10.1146/annurev-immunol-032713-120231.
126. Belardelli, F.; Gresser, I.; Maury, C.; Maunoury, M.T. Antitumor Effects of Interferon in Mice Injected with Interferon-Sensitive and Interferon-Resistant Friend Leukemia Cells. II. Role of Host Mechanisms. *Int. J. cancer* **1982**, *30*, 821–825, doi:10.1002/ijc.2910300622.

 doi:10.20944/preprints202507.2587.v1

127. Davidson, S.; Maini, M.K.; Wack, A. Disease-Promoting Effects of Type I Interferons in Viral, Bacterial, and Coinfections. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2015**, *35*, 252–264, doi:10.1089/jir.2014.0227.
128. Hussell, T.; Goulding, J. Structured Regulation of Inflammation during Respiratory Viral Infection. *Lancet. Infect. Dis.* **2010**, *10*, 360–366, doi:10.1016/S1473-3099(10)70067-0.
129. Sorrentino, L.; Fracella, M.; Frasca, F.; D'Auria, A.; Santinelli, L.; Maddaloni, L.; Bugani, G.; Bitossi, C.; Gentile, M.; Ceccarelli, G.; et al. Alterations in the Expression of IFN Lambda, IFN Gamma and Toll-like Receptors in Severe COVID-19 Patients. *Microorganisms* 2023, *11*.
130. Pasrija, R.; Naime, M. The Deregulated Immune Reaction and Cytokines Release Storm (CRS) in COVID-19 Disease. *Int. Immunopharmacol.* **2021**, *90*, 107225, doi:10.1016/j.intimp.2020.107225.
131. Fu, Y.; Cheng, Y.; Wu, Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Virol. Sin.* **2020**, *35*, 266–271, doi:10.1007/s12250-020-00207-4.
132. Moore, J.B.; June, C.H. Cytokine Release Syndrome in Severe COVID-19. *Science* **2020**, *368*, 473–474, doi:10.1126/science.abb8925.
133. Quan, C.; Li, C.; Ma, H.; Li, Y.; Zhang, H. Immunopathogenesis of Coronavirus-Induced Acute Respiratory Distress Syndrome (ARDS): Potential Infection-Associated Hemophagocytic Lymphohistiocytosis. *Clin. Microbiol. Rev.* **2020**, *34*, doi:10.1128/CMR.00074-20.
134. Kawai, T.; Akira, S. Toll-like Receptor and RIG-I-like Receptor Signaling. *Ann. N. Y. Acad. Sci.* **2008**, *1143*, 1–20, doi:10.1196/annals.1443.020.
135. Ebermeyer, T.; Cognasse, F.; Berthelot, P.; Mismetti, P.; Garraud, O.; Hamzeh-Cognasse, H. Platelet Innate Immune Receptors and TLRs: A Double-Edged Sword. *Int. J. Mol. Sci.* **2021**, *22*, doi:10.3390/ijms22157894.
136. Dajon, M.; Iribarren, K.; Cremer, I. Toll-like Receptor Stimulation in Cancer: A pro- and Anti-Tumor Double-Edged Sword. *Immunobiology* **2017**, *222*, 89–100, doi:10.1016/j.imbio.2016.06.009.
137. Harsini, S.; Beigy, M.; Akhavan-Sabbagh, M.; Rezaei, N. Toll-like Receptors in Lymphoid Malignancies: Double-Edged Sword. *Crit. Rev. Oncol. Hematol.* **2014**, *89*, 262–283, doi:10.1016/j.critrevonc.2013.08.010.
138. Yokota, S.-I.; Okabayashi, T.; Fujii, N. The Battle between Virus and Host: Modulation of Toll-like Receptor Signaling Pathways by Virus Infection. *Mediators Inflamm.* **2010**, *2010*, 184328, doi:10.1155/2010/184328.
139. Khanmohammadi, S.; Rezaei, N. Role of Toll-like Receptors in the Pathogenesis of COVID-19. *J. Med. Virol.* **2021**, *93*, 2735–2739, doi:10.1002/jmv.26826.
140. Yang, M.-Y.; Zheng, M.-H.; Meng, X.-T.; Ma, L.-W.; Liang, H.-Y.; Fan, H.-Y. Role of Toll-like Receptors in the Pathogenesis of COVID-19: Current and Future Perspectives. *Scand. J. Immunol.* **2023**, *98*, e13275, doi:https://doi.org/10.1111/sji.13275.
141. Mantovani, S.; Oliviero, B.; Varchetta, S.; Renieri, A.; Mondelli, M.U. TLRs: Innate Immune Sentries against SARS-CoV-2 Infection. *Int. J. Mol. Sci.* **2023**, *24*, doi:10.3390/ijms24098065.
142. Planès, R.; Bert, J.-B.; Tairi, S.; BenMohamed, L.; Bahraoui, E. SARS-CoV-2 Envelope (E) Protein Binds and Activates TLR2 Pathway: A Novel Molecular Target for COVID-19 Interventions. *Viruses* **2022**, *14*, doi:10.3390/v14050999.
143. Quagliariello, V.; Bonelli, A.; Caronna, A.; Lombari, M.C.; Conforti, G.; Libutti, M.; Iaffaioli, R. V; Berretta, M.; Botti, G.; Maurea, N. SARS-CoV-2 Infection: NLRP3 Inflammasome as Plausible Target to Prevent Cardiopulmonary Complications? *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 9169–9171, doi:10.26355/eurrev_202009_22867.
144. Landolina, N.; Ricci, B.; Veneziani, I.; Alicata, C.; Mariotti, F.R.; Pelosi, A.; Quatrini, L.; Mortari, E.P.; Carsetti, R.; Vacca, P.; et al. TLR2/4 Are Novel Activating Receptors for SARS-CoV-2 Spike Protein on NK Cells. *Front. Immunol.* **2024**, *15*, 1368946, doi:10.3389/fimmu.2024.1368946.

 doi:10.20944/preprints202507.2587.v1

145. Ghazanfari, D.; Courreges, M.C.; Belinski, L.E.; Hogrell, M.J.; Lloyd, J.; C. Bergmeier, S.; McCall, K.D.; Goetz, D.J. Mechanistic Insights into SARS-CoV-2 Spike Protein Induction of the Chemokine CXCL10. *Sci. Rep.* **2024**, *14*, 11179, doi:10.1038/s41598-024-61906-6.
146. Knoops, K.; Kikkert, M.; Worm, S.H.E. van den; Zevenhoven-Dobbe, J.C.; van der Meer, Y.; Koster, A.J.; Mommaas, A.M.; Snijder, E.J. SARS-Coronavirus Replication Is Supported by a Reticulovesicular Network of Modified Endoplasmic Reticulum. *PLoS Biol.* **2008**, *6*, e226, doi:10.1371/journal.pbio.0060226.
147. Han, L.; Zhuang, M.-W.; Deng, J.; Zheng, Y.; Zhang, J.; Nan, M.-L.; Zhang, X.-J.; Gao, C.; Wang, P.-H. SARS-CoV-2 ORF9b Antagonizes Type I and III Interferons by Targeting Multiple Components of the RIG-I/MDA-5-MAVS, TLR3-TRIF, and CGAS-STING Signaling Pathways. *J. Med. Virol.* **2021**, *93*, 5376–5389, doi:10.1002/jmv.27050.
148. Menezes, M.C.S.; Veiga, A.D.M.; Martins de Lima, T.; Kunimi Kubo Ariga, S.; Vieira Barbeiro, H.; de Lucena Moreira, C.; Pinto, A.A.S.; Brandao, R.A.; Marchini, J.F.; Alencar, J.C.; et al. Lower Peripheral Blood Toll-like Receptor 3 Expression Is Associated with an Unfavorable Outcome in Severe COVID-19 Patients. *Sci. Rep.* **2021**, *11*, 15223, doi:10.1038/s41598-021-94624-4.
149. Zhang, Q.; Bastard, P.; Liu, Z.; Le Pen, J.; Moncada-Velez, M.; Chen, J.; Ogishi, M.; Sabli, I.K.D.; Hodeib, S.; Korol, C.; et al. Inborn Errors of Type I IFN Immunity in Patients with Life-Threatening COVID-19. *Science* **2020**, *370*, doi:10.1126/science.abd4570.
150. Alseoudy, M.M.; Elgamal, M.; Abdelghany, D.A.; Borg, A.M.; El-Mesery, A.; Elzeiny, D.; Hammad, M.O. Prognostic Impact of Toll-like Receptors Gene Polymorphism on Outcome of COVID-19 Pneumonia: A Case-Control Study. *Clin. Immunol.* **2022**, *235*, 108929, doi:10.1016/j.clim.2022.108929.
151. Chomel, L.; Vogt, M.; Demiselle, J.; Le Borgne, P.; Tschirhart, M.; Morandeau, V.; Merdji, H.; Miguet, L.; Helms, J.; Meziani, F.; et al. TLRs1-10 Protein Expression in Circulating Human White Blood Cells during Bacterial and COVID-19 Infections. *J. Innate Immun.* 2024, *16*, 216–225.
152. Choudhury, A.; Mukherjee, S. In Silico Studies on the Comparative Characterization of the Interactions of SARS-CoV-2 Spike Glycoprotein with ACE-2 Receptor Homologs and Human TLRs. *J. Med. Virol.* **2020**, *92*, 2105–2113, doi:10.1002/jmv.25987.
153. Aboudounya, M.M.; Heads, R.J. COVID-19 and Toll-Like Receptor 4 (TLR4): SARS-CoV-2 May Bind and Activate TLR4 to Increase ACE2 Expression, Facilitating Entry and Causing Hyperinflammation. *Mediators Inflamm.* **2021**, *2021*, 8874339, doi:10.1155/2021/8874339.
154. Zhao, Y.; Kuang, M.; Li, J.; Zhu, L.; Jia, Z.; Guo, X.; Hu, Y.; Kong, J.; Yin, H.; Wang, X.; et al. SARS-CoV-2 Spike Protein Interacts with and Activates TLR41. *Cell Res.* 2021, *31*, 818–820.
155. Shirato, K.; Kizaki, T. SARS-CoV-2 Spike Protein S1 Subunit Induces pro-Inflammatory Responses via Toll-like Receptor 4 Signaling in Murine and Human Macrophages. *Heliyon* **2021**, *7*, e06187, doi:10.1016/j.heliyon.2021.e06187.
156. Giamarellos-Bourboulis, E.J.; Netea, M.G.; Rovina, N.; Akinosoglou, K.; Antoniadou, A.; Antonakos, N.; Damoraki, G.; Gkavogianni, T.; Adami, M.-E.; Katsaounou, P.; et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* **2020**, *27*, 992-1000.e3, doi:10.1016/j.chom.2020.04.009.
157. Richez, C.; Yasuda, K.; Watkins, A.A.; Akira, S.; Lafyatis, R.; van Seventer, J.M.; Rifkin, I.R. TLR4 Ligands Induce IFN-Alpha Production by Mouse Conventional Dendritic Cells and Human Monocytes after IFN-Beta Priming. *J. Immunol.* **2009**, *182*, 820–828, doi:10.4049/jimmunol.182.2.820.
158. Mukherjee, S.; Bayry, J. The Yin and Yang of TLR4 in COVID-19. *Cytokine Growth Factor Rev.* **2025**, *82*, 70–85, doi:10.1016/j.cytogfr.2024.10.001.
159. Durán-Méndez, A.; Aguilar-Arroyo, A.D.; Vivanco-Gómez, E.; Nieto-Ortega, E.; Pérez-Ortega, D.; Jiménez-

 doi:10.20944/preprints202507.2587.v1

Pérez, C.; Hernández-Skewes, K.Y.; Montiel-Bravo, G.; Roque-Reyes, O.J.; Romero-Lechuga, F.; et al. Tocilizumab Reduces COVID-19 Mortality and Pathology in a Dose and Timing-Dependent Fashion: A Multi-Centric Study. *Sci. Rep.* **2021**, *11*, 19728, doi:10.1038/s41598-021-99291-z.

160. Franzetti, M.; Forastieri, A.; Borsa, N.; Pandolfo, A.; Molteni, C.; Borghesi, L.; Pontiggia, S.; Evasi, G.; Guiotto, L.; Erba, M.; et al. IL-1 Receptor Antagonist Anakinra in the Treatment of COVID-19 Acute Respiratory Distress Syndrome: A Retrospective, Observational Study. *J. Immunol.* **2021**, *206*, 1569–1575, doi:10.4049/jimmunol.2001126.
161. Ng, B.; Cash-Mason, T.; Wang, Y.; Seitzer, J.; Burchard, J.; Brown, D.; Dudkin, V.; Davide, J.; Jadhav, V.; Sepp-Lorenzino, L.; et al. Intratracheal Administration of SiRNA Triggers MRNA Silencing in the Lung to Modulate T Cell Immune Response and Lung Inflammation. *Mol. Ther. Nucleic Acids* **2019**, *16*, 194–205, doi:10.1016/j.omtn.2019.02.013.
162. Asaba, C.N.; Ekabe, C.J.; Ayuk, H.S.; Gwanyama, B.N.; Bitazar, R.; Bukong, T.N. Interplay of TLR4 and SARS-CoV-2: Unveiling the Complex Mechanisms of Inflammation and Severity in COVID-19 Infections. *J. Inflamm. Res.* **2024**, *17*, 5077–5091, doi:10.2147/JIR.S474707.
163. Zhang, C.; Wang, X.; Wang, C.; He, C.; Ma, Q.; Li, J.; Wang, W.; Xu, Y.-T.; Wang, T. Qingwenzhike Prescription Alleviates Acute Lung Injury Induced by LPS via Inhibiting TLR4/NF-KB Pathway and NLRP3 Inflammasome Activation. *Front. Pharmacol.* **2021**, *12*, 790072, doi:10.3389/fphar.2021.790072.
164. Girkin, J.L.N.; Maltby, S.; Bartlett, N.W. Toll-like Receptor-Agonist-Based Therapies for Respiratory Viral Diseases: Thinking Outside the Cell. *Eur. Respir. Rev. an Off. J. Eur. Respir. Soc.* **2022**, *31*, doi:10.1183/16000617.0274-2021.
165. Lucas, C.; Wong, P.; Klein, J.; Castro, T.B.R.; Silva, J.; Sundaram, M.; Ellingson, M.K.; Mao, T.; Oh, J.E.; Israelow, B.; et al. Longitudinal Analyses Reveal Immunological Misfiring in Severe COVID-19. *Nature* **2020**, *584*, 463–469, doi:10.1038/s41586-020-2588-y.
166. Sohn, K.M.; Lee, S.G.; Kim, H.J.; Cheon, S.; Jeong, H.; Lee, J.; Kim, I.S.; Silwal, P.; Kim, Y.J.; Paik, S.; et al. COVID-19 Patients Upregulate Toll-like Receptor 4-Mediated Inflammatory Signaling That Mimics Bacterial Sepsis. *J. Korean Med. Sci.* **2020**, *35*, e343, doi:10.3346/jkms.2020.35.e343.
167. Fan, Y.; Guan, B.; Xu, J.; Zhang, H.; Yi, L.; Yang, Z. Role of Toll-like Receptor-Mediated Pyroptosis in Sepsis-Induced Cardiomyopathy. *Biomed. Pharmacother.* **2023**, *167*, 115493, doi:10.1016/j.biopha.2023.115493.
168. Kogan, E.A.; Berezovskiy, Y.S.; Blagova, O. V; Kukleva, A.D.; Bogacheva, G.A.; Kurilina, E. V; Kalinin, D. V; Bagdasaryan, T.R.; Semeyonova, L.A.; Gretsov, E.M.; et al. [Miocarditis in Patients with COVID-19 Confirmed by Immunohistochemical]. *Kardiologiia* **2020**, *60*, 4–10, doi:10.18087/cardio.2020.7.n1209.
169. van der Donk, L.E.H.; Bermejo-Jambrina, M.; van Hamme, J.L.; Volkers, M.M.W.; van Nuenen, A.C.; Kootstra, N.A.; Geijtenbeek, T.B.H. SARS-CoV-2 Suppresses TLR4-Induced Immunity by Dendritic Cells via C-Type Lectin Receptor DC-SIGN. *PLoS Pathog.* **2023**, *19*, e1011735, doi:10.1371/journal.ppat.1011735.
170. Cervantes-Barragan, L.; Züst, R.; Weber, F.; Spiegel, M.; Lang, K.S.; Akira, S.; Thiel, V.; Ludewig, B. Control of Coronavirus Infection through Plasmacytoid Dendritic-Cell-Derived Type I Interferon. *Blood* **2007**, *109*, 1131–1137, doi:10.1182/blood-2006-05-023770.
171. van der Sluis, R.M.; Cham, L.B.; Gris-Oliver, A.; Gammelgaard, K.R.; Pedersen, J.G.; Idorn, M.; Ahmadov, U.; Hernandez, S.S.; Cémalovic, E.; Godsk, S.H.; et al. TLR2 and TLR7 Mediate Distinct Immunopathological and Antiviral Plasmacytoid Dendritic Cell Responses to SARS-CoV-2 Infection. *EMBO J.* **2022**, *41*, e109622, doi:10.15252/embj.2021109622.
172. Metthew Lam, L.K.; Oatman, E.; Eckart, K.A.; Klingensmith, N.J.; Flowers, E.; Sayegh, L.; Yuen, J.; Clements, R.L.; Meyer, N.J.; Jurado, K.A.; et al. Human Red Blood Cells Express the RNA Sensor TLR7. *Sci. Rep.* **2024**, *14*, 15789, doi:10.1038/s41598-024-66410-5.

 doi:10.20944/preprints202507.2587.v1

173. Miquel, C.-H.; Abbas, F.; Cenac, C.; Foret-Lucas, C.; Guo, C.; Ducatez, M.; Joly, E.; Hou, B.; Guéry, J.-C. B Cell-Intrinsic TLR7 Signaling Is Required for Neutralizing Antibody Responses to SARS-CoV-2 and Pathogen-like COVID-19 Vaccines. *Eur. J. Immunol.* **2023**, *53*, e2350437, doi:10.1002/eji.202350437.
174. Bagheri-Hosseinabadi, Z.; Mohammadizadeh Ranjbar, F.; Nassiri, M.; Amiri, A.; Abbasifard, M. Nasopharyngeal Epithelial Cells from Patients with Coronavirus Disease 2019 Express Abnormal Levels of Toll-like Receptors. *Pathog. Glob. Health* **2023**, *117*, 401–408, doi:10.1080/20477724.2023.2166378.
175. Bagheri-Hosseinabadi, Z.; Rezazadeh Zarandi, E.; Mirabzadeh, M.; Amiri, A.; Abbasifard, M. MRNA Expression of Toll-like Receptors 3, 7, 8, and 9 in the Nasopharyngeal Epithelial Cells of Coronavirus Disease 2019 Patients. *BMC Infect. Dis.* **2022**, *22*, 448, doi:10.1186/s12879-022-07437-9.
176. Arefinia, N.; Banafi, P.; Zarezadeh, M.A.; Mousawi, H.S.; Yaghobi, R.; Farokhnia, M.; Sarvari, J. TLR3, TLR7, and TLR8 Genes Expression Datasets in COVID-19 Patients: Influences of the Disease Severity and Gender. *Data Br.* **2024**, *54*, 110498, doi:10.1016/j.dib.2024.110498.
177. Chidambaram, V.; Kumar, A.; Sadaf, M.I.; Lu, E.; Al'Aref, S.J.; Tarun, T.; Galiatsatos, P.; Gulati, M.; Blumenthal, R.S.; Leucker, T.M.; et al. COVID-19 in the Initiation and Progression of Atherosclerosis: Pathophysiology During and Beyond the Acute Phase. *JACC. Adv.* **2024**, *3*, 101107, doi:10.1016/j.jacadv.2024.101107.
178. Costa, T.J.; Potje, S.R.; Fraga-Silva, T.F.C.; da Silva-Neto, J.A.; Barros, P.R.; Rodrigues, D.; Machado, M.R.; Martins, R.B.; Santos-Eichler, R.A.; Benatti, M.N.; et al. Mitochondrial DNA and TLR9 Activation Contribute to SARS-CoV-2-Induced Endothelial Cell Damage. *Vascul. Pharmacol.* **2022**, *142*, 106946, doi:10.1016/j.vph.2021.106946.
179. Bezemer, G.F.G.; Garssen, J. TLR9 and COVID-19: A Multidisciplinary Theory of a Multifaceted Therapeutic Target. *Front. Pharmacol.* **2020**, *11*, 601685, doi:10.3389/fphar.2020.601685.
180. Delgado, J.M.; Pernas, L. Mitochondria as Sensors of Intracellular Pathogens. *Trends Endocrinol. Metab.* **2024**, doi:10.1016/j.tem.2024.10.009.
181. Zong, Y.; Li, H.; Liao, P.; Chen, L.; Pan, Y.; Zheng, Y.; Zhang, C.; Liu, D.; Zheng, M.; Gao, J. Mitochondrial Dysfunction: Mechanisms and Advances in Therapy. *Signal Transduct. Target. Ther.* **2024**, *9*, 124, doi:10.1038/s41392-024-01839-8.
182. Gay, L.; Desquiret-Dumas, V.; Nagot, N.; Rapenne, C.; Van de Perre, P.; Reynier, P.; Molès, J.-P. Long-Term Persistence of Mitochondrial Dysfunctions after Viral Infections and Antiviral Therapies: A Review of Mechanisms Involved. *J. Med. Virol.* **2024**, *96*, e29886, doi:10.1002/jmv.29886.
183. Romão, P.R.; Teixeira, P.C.; Schipper, L.; da Silva, I.; Santana Filho, P.; Júnior, L.C.R.; Peres, A.; Gonçalves da Fonseca, S.; Chagas Monteiro, M.; Lira, F.S.; et al. Viral Load Is Associated with Mitochondrial Dysfunction and Altered Monocyte Phenotype in Acute Severe SARS-CoV-2 Infection. *Int. Immunopharmacol.* **2022**, *108*, 108697, doi:10.1016/j.intimp.2022.108697.
184. Shi, C.-S.; Qi, H.-Y.; Boularan, C.; Huang, N.-N.; Abu-Asab, M.; Shelhamer, J.H.; Kehrl, J.H. SARS-Coronavirus Open Reading Frame-9b Suppresses Innate Immunity by Targeting Mitochondria and the MAVS/TRAF3/TRAF6 Signalosome. *J. Immunol.* **2014**, *193*, 3080–3089, doi:10.4049/jimmunol.1303196.
185. Oberemok, V. V; Laikova, K. V; Yurchenko, K.A.; Marochkin, N.A.; Fomochkina, I.I.; Kubyshkin, A. V SARS-CoV-2 Will Constantly Sweep Its Tracks: A Vaccine Containing CpG Motifs in "lasso" for the Multi-Faced Virus. *Inflamm. Res. Off. J. Eur. Histamine Res. Soc. ... [et al.]* **2020**, *69*, 801–812, doi:10.1007/s00011-020-01377-3.
186. Yang, J.-X.; Tseng, J.-C.; Tien, C.-F.; Lee, C.-Y.; Liu, Y.-L.; Lin, J.-J.; Tsai, P.-J.; Liao, H.-C.; Liu, S.-J.; Su, Y.-W.; et al. TLR9 and STING Agonists Cooperatively Boost the Immune Response to SARS-CoV-2 RBD Vaccine through an Increased Germinal Center B Cell Response and Reshaped T Helper Responses. *Int. J. Biol. Sci.*

 doi:10.20944/preprints202507.2587.v1

2023, *19*, 2897–2913, doi:10.7150/ijbs.81210.

187. Kouwaki, T.; Nishimura, T.; Wang, G.; Oshiumi, H. RIG-I-Like Receptor-Mediated Recognition of Viral Genomic RNA of Severe Acute Respiratory Syndrome Coronavirus-2 and Viral Escape From the Host Innate Immune Responses. *Front. Immunol.* **2021**, *12*, 700926, doi:10.3389/fimmu.2021.700926.
188. Thorne, L.G.; Reuschl, A.-K.; Zuliani-Alvarez, L.; Whelan, M.V.X.; Turner, J.; Noursadeghi, M.; Jolly, C.; Towers, G.J. SARS-CoV-2 Sensing by RIG-I and MDA5 Links Epithelial Infection to Macrophage Inflammation. *EMBO J.* **2021**, *40*, e107826, doi:10.15252/embj.2021107826.
189. Chang, H.; Hou, P.; Wang, X.; Xiang, A.; Wu, H.; Qi, W.; Yang, R.; Wang, X.; Li, X.; He, W.; et al. CD97 Negatively Regulates the Innate Immune Response against RNA Viruses by Promoting RNF125-Mediated RIG-I Degradation. *Cell. Mol. Immunol.* **2023**, *20*, 1457–1471, doi:10.1038/s41423-023-01103-z.
190. Yin, X.; Riva, L.; Pu, Y.; Martin-Sancho, L.; Kanamune, J.; Yamamoto, Y.; Sakai, K.; Gotoh, S.; Miorin, L.; De Jesus, P.D.; et al. MDA5 Governs the Innate Immune Response to SARS-CoV-2 in Lung Epithelial Cells. *Cell Rep.* **2021**, *34*, 108628, doi:10.1016/j.celrep.2020.108628.
191. Rebendenne, A.; Valadão, A.L.C.; Tauziet, M.; Maarifi, G.; Bonaventure, B.; McKellar, J.; Planès, R.; Nisole, S.; Arnaud-Arnould, M.; Moncorgé, O.; et al. SARS-CoV-2 Triggers an MDA-5-Dependent Interferon Response Which Is Unable to Control Replication in Lung Epithelial Cells. *J. Virol.* **2021**, *95*, doi:10.1128/JVI.02415-20.
192. Yang, D.-M.; Geng, T.-T.; Harrison, A.G.; Wang, P.-H. Differential Roles of RIG-I like Receptors in SARS-CoV-2 Infection. *Mil. Med. Res.* 2021, *8*, 49.
193. Nahavandi-Parizi, P.; Kariminik, A.; Montazeri, M. Retinoic Acid-Inducible Gene 1 (RIG-1) and IFN-β Promoter Stimulator-1 (IPS-1) Significantly down-Regulated in the Severe Coronavirus Disease 2019 (COVID-19). *Mol. Biol. Rep.* **2023**, *50*, 907–911, doi:10.1007/s11033-022-07981-2.
194. Rice, M.; Tili, E.; Loghmani, H.; Nuovo, G.J. The Differential Expression of Toll like Receptors and RIG-1 Correlates to the Severity of Infectious Diseases. *Ann. Diagn. Pathol.* **2023**, *63*, 152102, doi:10.1016/j.anndiagpath.2022.152102.
195. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271-280.e8, doi:10.1016/j.cell.2020.02.052.
196. Sampaio, N.G.; Chauveau, L.; Hertzog, J.; Bridgeman, A.; Fowler, G.; Moonen, J.P.; Dupont, M.; Russell, R.A.; Noerenberg, M.; Rehwinkel, J. The RNA Sensor MDA5 Detects SARS-CoV-2 Infection. *Sci. Rep.* **2021**, *11*, 13638, doi:10.1038/s41598-021-92940-3.
197. Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V. V; Guo, J.Z.; Swaney, D.L.; et al. A SARS-CoV-2 Protein Interaction Map Reveals Targets for Drug Repurposing. *Nature* **2020**, *583*, 459–468, doi:10.1038/s41586-020-2286-9.
198. Wang, L.; Zhu, Y.; Zhang, N.; Xian, Y.; Tang, Y.; Ye, J.; Reza, F.; He, G.; Wen, X.; Jiang, X. The Multiple Roles of Interferon Regulatory Factor Family in Health and Disease. *Signal Transduct. Target. Ther.* **2024**, *9*, 282, doi:10.1038/s41392-024-01980-4.
199. Sanchez David, R.Y.; Combredet, C.; Najburg, V.; Millot, G.A.; Beauclair, G.; Schwikowski, B.; Léger, T.; Camadro, J.-M.; Jacob, Y.; Bellalou, J.; et al. LGP2 Binds to PACT to Regulate RIG-I- and MDA5-Mediated Antiviral Responses. *Sci. Signal.* **2019**, *12*, doi:10.1126/scisignal.aar3993.
200. Rodriguez, K.R.; Bruns, A.M.; Horvath, C.M. MDA5 and LGP2: Accomplices and Antagonists of Antiviral Signal Transduction. *J. Virol.* **2014**, *88*, 8194–8200, doi:10.1128/JVI.00640-14.
201. Liu, G.; Lee, J.-H.; Parker, Z.M.; Acharya, D.; Chiang, J.J.; van Gent, M.; Riedl, W.; Davis-Gardner, M.E.; Wies, E.; Chiang, C.; et al. ISG15-Dependent Activation of the Sensor MDA5 Is Antagonized by the SARS-

 doi:10.20944/preprints202507.2587.v1

CoV-2 Papain-like Protease to Evade Host Innate Immunity. *Nat. Microbiol.* **2021**, *6*, 467–478, doi:10.1038/s41564-021-00884-1.

202. Sacchi, A.; Giannessi, F.; Sabatini, A.; Percario, Z.A.; Affabris, E. SARS-CoV-2 Evasion of the Interferon System: Can We Restore Its Effectiveness? *Int. J. Mol. Sci.* **2023**, *24*, doi:10.3390/ijms24119353.
203. Kim, Y.; Park, J.; Kim, S.; Kim, M.; Kang, M.-G.; Kwak, C.; Kang, M.; Kim, B.; Rhee, H.-W.; Kim, V.N. PKR Senses Nuclear and Mitochondrial Signals by Interacting with Endogenous Double-Stranded RNAs. *Mol. Cell* **2018**, *71*, 1051-1063.e6, doi:10.1016/j.molcel.2018.07.029.
204. Gal-Ben-Ari, S.; Barrera, I.; Ehrlich, M.; Rosenblum, K. PKR: A Kinase to Remember. *Front. Mol. Neurosci.* **2018**, *11*, 480, doi:10.3389/fnmol.2018.00480.
205. Melchjorsen, J.; Kristiansen, H.; Christiansen, R.; Rintahaka, J.; Matikainen, S.; Paludan, S.R.; Hartmann, R. Differential Regulation of the OASL and OAS1 Genes in Response to Viral Infections. *J. Interf. cytokine Res. Off. J. Int. Soc. Interf. Cytokine Res.* **2009**, *29*, 199–207, doi:10.1089/jir.2008.0050.
206. Li, Y.; Renner, D.M.; Comar, C.E.; Whelan, J.N.; Reyes, H.M.; Cardenas-Diaz, F.L.; Truitt, R.; Tan, L.H.; Dong, B.; Alysandratos, K.D.; et al. SARS-CoV-2 Induces Double-Stranded RNA-Mediated Innate Immune Responses in Respiratory Epithelial-Derived Cells and Cardiomyocytes. *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, doi:10.1073/pnas.2022643118.
207. Lee, D.; Le Pen, J.; Yatim, A.; Dong, B.; Aquino, Y.; Ogishi, M.; Pescarmona, R.; Talouarn, E.; Rinchai, D.; Zhang, P.; et al. Inborn Errors of OAS-RNase L in SARS-CoV-2-Related Multisystem Inflammatory Syndrome in Children. *Science* **2023**, *379*, eabo3627, doi:10.1126/science.abo3627.
208. Aloise, C.; Schipper, J.G.; van Vliet, A.; Oymans, J.; Donselaar, T.; Hurdiss, D.L.; de Groot, R.J.; van Kuppeveld, F.J.M. SARS-CoV-2 Nucleocapsid Protein Inhibits the PKR-Mediated Integrated Stress Response through RNA-Binding Domain N2b. *PLoS Pathog.* **2023**, *19*, e1011582, doi:10.1371/journal.ppat.1011582.
209. Christ, W.; Klingström, J.; Tynell, J. SARS-CoV-2 Variant-Specific Differences in Inhibiting the Effects of the PKR-Activated Integrated Stress Response. *Virus Res.* **2024**, *339*, 199271, doi:10.1016/j.virusres.2023.199271.
210. Chan, Y.-H.; Lundberg, V.; Le Pen, J.; Yuan, J.; Lee, D.; Pinci, F.; Volpi, S.; Nakajima, K.; Bondet, V.; Åkesson, S.; et al. SARS-CoV-2 Brainstem Encephalitis in Human Inherited DBR1 Deficiency. *J. Exp. Med.* **2024**, *221*, e20231725, doi:10.1084/jem.20231725.
211. Ru, S.; Tang, S.; Xu, H.; Yin, J.; Guo, Y.; Song, L.; Jin, Z.; Lee, D.; Chan, Y.-H.; Chen, X.; et al. Human DBR1 Deficiency Impairs Stress Granule–Dependent PKR Antiviral Immunity. *J. Exp. Med.* **2024**, *222*, e20240010, doi:10.1084/jem.20240010.
212. Wang, B.; Tian, Y.; Yin, Q. AIM2 Inflammasome Assembly and Signaling. *Adv. Exp. Med. Biol.* **2019**, *1172*, 143–155, doi:10.1007/978-981-13-9367-9_7.
213. Jiang, Z.; Wei, F.; Zhang, Y.; Wang, T.; Gao, W.; Yu, S.; Sun, H.; Pu, J.; Sun, Y.; Wang, M.; et al. IFI16 Directly Senses Viral RNA and Enhances RIG-I Transcription and Activation to Restrict Influenza Virus Infection. *Nat. Microbiol.* **2021**, *6*, 932–945, doi:10.1038/s41564-021-00907-x.
214. Hamldar, S.; Kiani, S.J.; Khoshmirsafa, M.; Nahand, J.S.; Mirzaei, H.; Khatami, A.; Kahyesh-Esfandiary, R.; Khanaliha, K.; Tavakoli, A.; Babakhaniyan, K.; et al. Expression Profiling of Inflammation-Related Genes Including IFI-16, NOTCH2, CXCL8, THBS1 in COVID-19 Patients. *Biol. J. Int. Assoc. Biol. Stand.* **2022**, *80*, 27–34, doi:10.1016/j.biologicals.2022.09.001.
215. Yang, C.-A.; Huang, Y.-L.; Chiang, B.-L. Innate Immune Response Analysis in COVID-19 and Kawasaki Disease Reveals MIS-C Predictors. *J. Formos. Med. Assoc.* **2022**, *121*, 623–632, doi:10.1016/j.jfma.2021.06.009.
216. Man, S.M.; Karki, R.; Kanneganti, T.-D. AIM2 Inflammasome in Infection, Cancer, and Autoimmunity: Role in DNA Sensing, Inflammation, and Innate Immunity. *Eur. J. Immunol.* **2016**, *46*, 269–280,

 doi:10.20944/preprints202507.2587.v1

doi:10.1002/eji.201545839.

217. Junqueira, C.; Crespo, Â.; Ranjbar, S.; de Lacerda, L.B.; Lewandrowski, M.; Ingber, J.; Parry, B.; Ravid, S.; Clark, S.; Schrimpf, M.R.; et al. FcγR-Mediated SARS-CoV-2 Infection of Monocytes Activates Inflammation. *Nature* **2022**, *606*, 576–584, doi:10.1038/s41586-022-04702-4.
218. Hadjadj, J.; Yatim, N.; Barnabei, L.; Corneau, A.; Boussier, J.; Smith, N.; Péré, H.; Charbit, B.; Bondet, V.; Chenevier-Gobeaux, C.; et al. Impaired Type I Interferon Activity and Inflammatory Responses in Severe COVID-19 Patients. *Science* **2020**, *369*, 718–724, doi:10.1126/science.abc6027.
219. Rodrigues, T.S.; de Sá, K.S.G.; Ishimoto, A.Y.; Becerra, A.; Oliveira, S.; Almeida, L.; Gonçalves, A. V; Perucello, D.B.; Andrade, W.A.; Castro, R.; et al. Inflammasomes Are Activated in Response to SARS-CoV-2 Infection and Are Associated with COVID-19 Severity in Patients. *J. Exp. Med.* **2021**, *218*, doi:10.1084/jem.20201707.
220. Chan, A.H.; Schroder, K. Inflammasome Signaling and Regulation of Interleukin-1 Family Cytokines. *J. Exp. Med.* **2020**, *217*, doi:10.1084/jem.20190314.
221. Decout, A.; Katz, J.D.; Venkatraman, S.; Ablasser, A. The CGAS-STING Pathway as a Therapeutic Target in Inflammatory Diseases. *Nat. Rev. Immunol.* **2021**, *21*, 548–569, doi:10.1038/s41577-021-00524-z.
222. Wu, Y.; Zhang, M.; Yuan, C.; Ma, Z.; Li, W.; Zhang, Y.; Su, L.; Xu, J.; Liu, W. Progress of CGAS-STING Signaling in Response to SARS-CoV-2 Infection. *Front. Immunol.* **2022**, *13*, 1010911, doi:10.3389/fimmu.2022.1010911.
223. Rui, Y.; Su, J.; Shen, S.; Hu, Y.; Huang, D.; Zheng, W.; Lou, M.; Shi, Y.; Wang, M.; Chen, S.; et al. Unique and Complementary Suppression of CGAS-STING and RNA Sensing- Triggered Innate Immune Responses by SARS-CoV-2 Proteins. *Signal Transduct. Target. Ther.* **2021**, *6*, 123, doi:10.1038/s41392-021-00515-5.
224. Humphries, F.; Shmuel-Galia, L.; Jiang, Z.; Wilson, R.; Landis, P.; Ng, S.-L.; Parsi, K.-M.; Maehr, R.; Cruz, J.; Morales-Ramos, A.; et al. A Diamidobenzimidazole STING Agonist Protects against SARS-CoV-2 Infection. *Sci. Immunol.* **2021**, *6*, doi:10.1126/sciimmunol.abi9002.
225. Li, M.; Ferretti, M.; Ying, B.; Descamps, H.; Lee, E.; Dittmar, M.; Lee, J.S.; Whig, K.; Kamalia, B.; Dohnalová, L.; et al. Pharmacological Activation of STING Blocks SARS-CoV-2 Infection. *Sci. Immunol.* **2021**, *6*, doi:10.1126/sciimmunol.abi9007.
226. Domizio, J. Di; Gulen, M.F.; Saidoune, F.; Thacker, V. V; Yatim, A.; Sharma, K.; Nass, T.; Guenova, E.; Schaller, M.; Conrad, C.; et al. The CGAS-STING Pathway Drives Type I IFN Immunopathology in COVID-19. *Nature* **2022**, *603*, 145–151, doi:10.1038/s41586-022-04421-w.
227. Li, H.; Zhou, F.; Zhang, L. STING, a Critical Contributor to SARS-CoV-2 Immunopathology. *Signal Transduct. Target. Ther.* **2022**, *7*, 106, doi:10.1038/s41392-022-00967-3.
228. Xiao, R.; Zhang, A. Involvement of the STING Signaling in COVID-19. *Front. Immunol.* **2022**, *13*, 1006395, doi:10.3389/fimmu.2022.1006395.
229. Marino, G.; Zhang, B.; Schmitz, A.; Schwensen, H.V.; Reinert, L.S.; Paludan, S.R. STING Is Redundant for Host Defense and Pathology of COVID-19-like Disease in Mice. *Life Sci. alliance* **2023**, *6*, doi:10.26508/lsa.202301997.
230. Queiroz, M.A.F.; Brito, W.R.D.S.; Pereira, K.A.S.; Pereira, L.M.S.; Amoras, E. da S.G.; Lima, S.S.; Santos, E.F. Dos; Costa, F.P. da; Sarges, K.M.L. de; Cantanhede, M.H.D.; et al. Severe COVID-19 and Long COVID Are Associated with High Expression of STING, CGAS and IFN-α. *Sci. Rep.* **2024**, *14*, 4974, doi:10.1038/s41598-024-55696-0.
231. Neufeldt, C.J.; Cerikan, B.; Cortese, M.; Frankish, J.; Lee, J.-Y.; Plociennikowska, A.; Heigwer, F.; Prasad, V.; Joecks, S.; Burkart, S.S.; et al. SARS-CoV-2 Infection Induces a pro-Inflammatory Cytokine Response through CGAS-STING and NF-KB. *Commun. Biol.* **2022**, *5*, 45, doi:10.1038/s42003-021-02983-5.

 doi:10.20944/preprints202507.2587.v1

232. Zhou, Z.; Zhang, X.; Lei, X.; Xiao, X.; Jiao, T.; Ma, R.; Dong, X.; Jiang, Q.; Wang, W.; Shi, Y.; et al. Sensing of Cytoplasmic Chromatin by CGAS Activates Innate Immune Response in SARS-CoV-2 Infection. *Signal Transduct. Target. Ther.* **2021**, *6*, 382, doi:10.1038/s41392-021-00800-3.
233. Znaidia, M.; Demeret, C.; van der Werf, S.; Komarova, A. V Characterization of SARS-CoV-2 Evasion: Interferon Pathway and Therapeutic Options. *Viruses* **2022**, *14*, doi:10.3390/v14061247.
234. Finkel, Y.; Mizrahi, O.; Nachshon, A.; Weingarten-Gabbay, S.; Morgenstern, D.; Yahalom-Ronen, Y.; Tamir, H.; Achdout, H.; Stein, D.; Israeli, O.; et al. The Coding Capacity of SARS-CoV-2. *Nature* **2021**, *589*, 125–130, doi:10.1038/s41586-020-2739-1.
235. Viswanathan, T.; Arya, S.; Chan, S.-H.; Qi, S.; Dai, N.; Misra, A.; Park, J.-G.; Oladunni, F.; Kovalskyy, D.; Hromas, R.A.; et al. Structural Basis of RNA Cap Modification by SARS-CoV-2. *Nat. Commun.* **2020**, *11*, 3718, doi:10.1038/s41467-020-17496-8.
236. Daffis, S.; Szretter, K.J.; Schriewer, J.; Li, J.; Youn, S.; Errett, J.; Lin, T.-Y.; Schneller, S.; Zust, R.; Dong, H.; et al. 2′-O Methylation of the Viral MRNA Cap Evades Host Restriction by IFIT Family Members. *Nature* **2010**, *468*, 452–456, doi:10.1038/nature09489.
237. Hackbart, M.; Deng, X.; Baker, S.C. Coronavirus Endoribonuclease Targets Viral Polyuridine Sequences to Evade Activating Host Sensors. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 8094–8103, doi:10.1073/pnas.1921485117.
238. Romano, M.; Ruggiero, A.; Squeglia, F.; Maga, G.; Berisio, R. A Structural View of SARS-CoV-2 RNA Replication Machinery: RNA Synthesis, Proofreading and Final Capping. *Cells* **2020**, *9*, doi:10.3390/cells9051267.
239. Zheng, Y.; Zhuang, M.-W.; Han, L.; Zhang, J.; Nan, M.-L.; Zhan, P.; Kang, D.; Liu, X.; Gao, C.; Wang, P.-H. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Membrane (M) Protein Inhibits Type I and III Interferon Production by Targeting RIG-I/MDA-5 Signaling. *Signal Transduct. Target. Ther.* **2020**, *5*, 299, doi:10.1038/s41392-020-00438-7.
240. Oh, S.J.; Shin, O.S. SARS-CoV-2 Nucleocapsid Protein Targets RIG-I-Like Receptor Pathways to Inhibit the Induction of Interferon Response. *Cells* **2021**, *10*, doi:10.3390/cells10030530.
241. Gutmann, T.; Kuster, D.; Hyman, A.A. SARS-CoV-2 Nucleocapsid Protein Directly Prevents CGAS-DNA Recognition through Competitive Binding. *Proc. Natl. Acad. Sci. U. S. A.* **2025**, *122*, e2426204122, doi:10.1073/pnas.2426204122.
242. Wu, Y.; Ma, L.; Zhuang, Z.; Cai, S.; Zhao, Z.; Zhou, L.; Zhang, J.; Wang, P.-H.; Zhao, J.; Cui, J. Main Protease of SARS-CoV-2 Serves as a Bifunctional Molecule in Restricting Type I Interferon Antiviral Signaling. *Signal Transduct. Target. Ther.* **2020**, *5*, 221, doi:10.1038/s41392-020-00332-2.
243. Jiang, H.-W.; Zhang, H.-N.; Meng, Q.-F.; Xie, J.; Li, Y.; Chen, H.; Zheng, Y.-X.; Wang, X.-N.; Qi, H.; Zhang, J.; et al. SARS-CoV-2 Orf9b Suppresses Type I Interferon Responses by Targeting TOM70. *Cell. Mol. Immunol.* **2020**, *17*, 998–1000, doi:10.1038/s41423-020-0514-8.
244. Liu, Y.; Qin, C.; Rao, Y.; Ngo, C.; Feng, J.J.; Zhao, J.; Zhang, S.; Wang, T.-Y.; Carriere, J.; Savas, A.C.; et al. SARS-CoV-2 Nsp5 Demonstrates Two Distinct Mechanisms Targeting RIG-I and MAVS To Evade the Innate Immune Response. *MBio* **2021**, *12*, e0233521, doi:10.1128/mBio.02335-21.
245. Zhu, Y.; Zhang, Z.; Song, J.; Qian, W.; Gu, X.; Yang, C.; Shen, N.; Xue, F.; Tang, Y. SARS-CoV-2-Encoded MiRNAs Inhibit Host Type I Interferon Pathway and Mediate Allelic Differential Expression of Susceptible Gene. *Front. Immunol.* **2021**, *12*, 767726, doi:10.3389/fimmu.2021.767726.
246. Xia, H.; Cao, Z.; Xie, X.; Zhang, X.; Chen, J.Y.-C.; Wang, H.; Menachery, V.D.; Rajsbaum, R.; Shi, P.-Y. Evasion of Type I Interferon by SARS-CoV-2. *Cell Rep.* **2020**, *33*, 108234, doi:10.1016/j.celrep.2020.108234.
247. Shin, D.; Mukherjee, R.; Grewe, D.; Bojkova, D.; Baek, K.; Bhattacharya, A.; Schulz, L.; Widera, M.;

 doi:10.20944/preprints202507.2587.v1

Mehdipour, A.R.; Tascher, G.; et al. Papain-like Protease Regulates SARS-CoV-2 Viral Spread and Innate Immunity. *Nature* **2020**, *587*, 657–662, doi:10.1038/s41586-020-2601-5.

248. Moustaqil, M.; Ollivier, E.; Chiu, H.-P.; Van Tol, S.; Rudolffi-Soto, P.; Stevens, C.; Bhumkar, A.; Hunter, D.J.B.; Freiberg, A.N.; Jacques, D.; et al. SARS-CoV-2 Proteases PLpro and 3CLpro Cleave IRF3 and Critical Modulators of Inflammatory Pathways (NLRP12 and TAB1): Implications for Disease Presentation across Species. *Emerg. Microbes Infect.* **2021**, *10*, 178–195, doi:10.1080/22221751.2020.1870414.
249. Li, A.; Zhao, K.; Zhang, B.; Hua, R.; Fang, Y.; Jiang, W.; Zhang, J.; Hui, L.; Zheng, Y.; Li, Y.; et al. SARS-CoV-2 NSP12 Protein Is Not an Interferon-β Antagonist. *J. Virol.* **2021**, *95*, e0074721, doi:10.1128/JVI.00747-21.
250. Vazquez, C.; Swanson, S.E.; Negatu, S.G.; Dittmar, M.; Miller, J.; Ramage, H.R.; Cherry, S.; Jurado, K.A. SARS-CoV-2 Viral Proteins NSP1 and NSP13 Inhibit Interferon Activation through Distinct Mechanisms. *PLoS One* **2021**, *16*, e0253089, doi:10.1371/journal.pone.0253089.
251. Yuen, C.-K.; Lam, J.-Y.; Wong, W.-M.; Mak, L.-F.; Wang, X.; Chu, H.; Cai, J.-P.; Jin, D.-Y.; To, K.K.-W.; Chan, J.F.-W.; et al. SARS-CoV-2 Nsp13, Nsp14, Nsp15 and Orf6 Function as Potent Interferon Antagonists. *Emerg. Microbes Infect.* **2020**, *9*, 1418–1428, doi:10.1080/22221751.2020.1780953.
252. Banerjee, A.K.; Blanco, M.R.; Bruce, E.A.; Honson, D.D.; Chen, L.M.; Chow, A.; Bhat, P.; Ollikainen, N.; Quinodoz, S.A.; Loney, C.; et al. SARS-CoV-2 Disrupts Splicing, Translation, and Protein Trafficking to Suppress Host Defenses. *Cell* **2020**, *183*, 1325-1339.e21, doi:10.1016/j.cell.2020.10.004.
253. Rashid, F.; Dzakah, E.E.; Wang, H.; Tang, S. The ORF8 Protein of SARS-CoV-2 Induced Endoplasmic Reticulum Stress and Mediated Immune Evasion by Antagonizing Production of Interferon Beta. *Virus Res.* **2021**, *296*, 198350, doi:10.1016/j.virusres.2021.198350.
254. Miorin, L.; Kehrer, T.; Sanchez-Aparicio, M.T.; Zhang, K.; Cohen, P.; Patel, R.S.; Cupic, A.; Makio, T.; Mei, M.; Moreno, E.; et al. SARS-CoV-2 Orf6 Hijacks Nup98 to Block STAT Nuclear Import and Antagonize Interferon Signaling. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 28344–28354, doi:10.1073/pnas.2016650117.
255. Konno, Y.; Kimura, I.; Uriu, K.; Fukushi, M.; Irie, T.; Koyanagi, Y.; Sauter, D.; Gifford, R.J.; Nakagawa, S.; Sato, K. SARS-CoV-2 ORF3b Is a Potent Interferon Antagonist Whose Activity Is Increased by a Naturally Occurring Elongation Variant. *Cell Rep.* **2020**, *32*, 108185, doi:10.1016/j.celrep.2020.108185.
256. Li, D.; Wu, M. Pattern Recognition Receptors in Health and Diseases. *Signal Transduct. Target. Ther.* **2021**, *6*, 291, doi:10.1038/s41392-021-00687-0.
257. Choudhury, A.; Das, N.C.; Patra, R.; Mukherjee, S. In Silico Analyses on the Comparative Sensing of SARS-CoV-2 MRNA by the Intracellular TLRs of Humans. *J. Med. Virol.* **2021**, *93*, 2476–2486, doi:10.1002/jmv.26776.
258. Kayesh, M.E.H.; Kohara, M.; Tsukiyama-Kohara, K. An Overview of Recent Insights into the Response of TLR to SARS-CoV-2 Infection and the Potential of TLR Agonists as SARS-CoV-2 Vaccine Adjuvants. *Viruses* **2021**, *13*, doi:10.3390/v13112302.
259. Zhou, S.-H.; Zhang, R.-Y.; Zhang, H.-W.; Liu, Y.-L.; Wen, Y.; Wang, J.; Li, Y.-T.; You, Z.-W.; Yin, X.-G.; Qiu, H.; et al. RBD Conjugate Vaccine with a Built-in TLR1/2 Agonist Is Highly Immunogenic against SARS-CoV-2 and Variants of Concern. *Chem. Commun. (Camb).* **2022**, *58*, 2120–2123, doi:10.1039/d1cc06520c.
260. Cojocaru, E.; Cojocaru, C.; Antoniu, S.A.; Stafie, C.S.; Rajnoveanu, A.; Rajnoveanu, R.-M. Inhaled Interferons Beta and SARS-COV2 Infection: A Preliminary Therapeutic Perspective. *Expert Rev. Respir. Med.* **2022**, *16*, 257–261, doi:10.1080/17476348.2022.2008910.
261. Tamir, H.; Melamed, S.; Erez, N.; Politi, B.; Yahalom-Ronen, Y.; Achdout, H.; Lazar, S.; Gutman, H.; Avraham, R.; Weiss, S.; et al. Induction of Innate Immune Response by TLR3 Agonist Protects Mice against SARS-CoV-2 Infection. *Viruses* **2022**, *14*, doi:10.3390/v14020189.
262. Kircheis, R. In Silico Analyses Indicate a Lower Potency for Dimerization of TLR4/MD-2 as the Reason

 doi:10.20944/preprints202507.2587.v1

for the Lower Pathogenicity of Omicron Compared to Wild-Type Virus and Earlier SARS-CoV-2 Variants. *Int. J. Mol. Sci.* **2024**, *25*, doi:10.3390/ijms25105451.

263. Jiang, Y.; Zhao, T.; Zhou, X.; Xiang, Y.; Gutierrez-Castrellon, P.; Ma, X. Inflammatory Pathways in COVID-19: Mechanism and Therapeutic Interventions. *MedComm* **2022**, *3*, e154, doi:10.1002/mco2.154.
264. McKinnon, J.E.; Santiaguel, J.; Murta de Oliveira, C.; Yu, D.; Khursheed, M.; Moreau, F.; Klopp-Schulze, L.; Shaw, J.; Roy, S.; Kao, A.H. Enpatoran in COVID-19 Pneumonia: Safety and Efficacy Results from a Phase II Randomized Trial. *Clin. Transl. Sci.* **2023**, *16*, 2640–2653, doi:10.1111/cts.13658.
265. Farooq, M.; Khan, A.W.; Ahmad, B.; Kim, M.S.; Choi, S. Therapeutic Targeting of Innate Immune Receptors Against SARS-CoV-2 Infection. *Front. Pharmacol.* **2022**, *13*, 915565, doi:10.3389/fphar.2022.915565.
266. Marx, S.; Kümmerer, B.M.; Grützner, C.; Kato, H.; Schlee, M.; Renn, M.; Bartok, E.; Hartmann, G. RIG-I-Induced Innate Antiviral Immunity Protects Mice from Lethal SARS-CoV-2 Infection. *Mol. Ther. Nucleic Acids* **2022**, *27*, 1225–1234, doi:10.1016/j.omtn.2022.02.008.
267. Mao, T.; Israelow, B.; Lucas, C.; Vogels, C.B.F.; Gomez-Calvo, M.L.; Fedorova, O.; Breban, M.I.; Menasche, B.L.; Dong, H.; Linehan, M.; et al. A Stem-Loop RNA RIG-I Agonist Protects against Acute and Chronic SARS-CoV-2 Infection in Mice. *J. Exp. Med.* **2022**, *219*, doi:10.1084/jem.20211818.
268. Lozhkov, A.A.; Plotnikova, M.A.; Egorova, M.A.; Baranovskaya, I.L.; Elpaeva, E.A.; Klotchenko, S.A.; Vasin, A. V Simultaneous Detection of RIG-1, MDA5, and IFIT-1 Expression Is a Convenient Tool for Evaluation of the Interferon-Mediated Response. *Viruses* **2022**, *14*, doi:10.3390/v14102090.
269. Jin, R.; Cao, X.; Lu, M.; Gao, Q.; Ma, T. The Intersection Molecule MDA5 in Cancer and COVID-19. *Front. Immunol.* **2022**, *13*, 963051, doi:10.3389/fimmu.2022.963051.
270. Qi, H.; Ma, Q.-H.; Feng, W.; Chen, S.-M.; Wu, C.-S.; Wang, Y.; Wang, T.-X.; Hou, Y.-L.; Jia, Z.-H. Glycyrrhetinic Acid Blocks SARS-CoV-2 Infection by Activating the CGAS-STING Signalling Pathway. *Br. J. Pharmacol.* **2024**, *181*, 3976–3992, doi:10.1111/bph.16473.
271. Parums, D. V Long COVID or Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) and the Urgent Need to Identify Diagnostic Biomarkers and Risk Factors. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2024**, *30*, e946512, doi:10.12659/MSM.946512.
272. Fracella, M.; Mancino, E.; Nenna, R.; Virgillito, C.; Frasca, F.; D'Auria, A.; Sorrentino, L.; Petrarca, L.; La Regina, D.; Matera, L.; et al. Age-Related Transcript Changes in Type I Interferon Signaling in Children and Adolescents with Long COVID. *Eur. J. Immunol.* **2024**, *54*, e2350682, doi:10.1002/eji.202350682.
273. Hope, A.A.; Evering, T.H. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Infect. Dis. Clin. North Am.* **2022**, *36*, 379–395, doi:10.1016/j.idc.2022.02.004.
274. Umakanthan, S.; Katwaroo, A.R.; Bukelo, M.; Bg, S.; Boralingaiah, P.; Ranade, A. V; Rangan, P.; Shashidhar, S.; Kini, J.R.; Kini, G. Post-Acute Sequelae of Covid-19: A System-Wise Approach on the Effects of Long-Covid-19. *Am. J. Med. open* **2024**, *12*, 100071, doi:10.1016/j.ajmo.2024.100071.
275. Konno, H.; Konno, K.; Barber, G.N. Cyclic Dinucleotides Trigger ULK1 (ATG1) Phosphorylation of STING to Prevent Sustained Innate Immune Signaling. *Cell* **2013**, *155*, 688–698, doi:10.1016/j.cell.2013.09.049.
276. Ablasser, A.; Chen, Z.J. CGAS in Action: Expanding Roles in Immunity and Inflammation. *Science* **2019**, *363*, doi:10.1126/science.aat8657.
277. Taquet, M.; Sillett, R.; Zhu, L.; Mendel, J.; Camplisson, I.; Dercon, Q.; Harrison, P.J. Neurological and Psychiatric Risk Trajectories after SARS-CoV-2 Infection: An Analysis of 2-Year Retrospective Cohort Studies Including 1 284 437 Patients. *The lancet. Psychiatry* **2022**, *9*, 815–827, doi:10.1016/S2215-0366(22)00260-7.
278. Davis, H.E.; Assaf, G.S.; McCorkell, L.; Wei, H.; Low, R.J.; Re'em, Y.; Redfield, S.; Austin, J.P.; Akrami, A. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact.

 doi:10.20944/preprints202507.2587.v1

EClinicalMedicine **2021**, *38*, 101019, doi:10.1016/j.eclinm.2021.101019.

279. Damiano, R.F.; Rocca, C.C. de A.; Serafim, A. de P.; Loftis, J.M.; Talib, L.L.; Pan, P.M.; Cunha-Neto, E.; Kalil, J.; de Castro, G.S.; Seelaender, M.; et al. Cognitive Impairment in Long-COVID and Its Association with Persistent Dysregulation in Inflammatory Markers. *Front. Immunol.* **2023**, *14*, 1174020, doi:10.3389/fimmu.2023.1174020.
280. Fontes-Dantas, F.L.; Fernandes, G.G.; Gutman, E.G.; De Lima, E. V; Antonio, L.S.; Hammerle, M.B.; Mota-Araujo, H.P.; Colodeti, L.C.; Araújo, S.M.B.; Froz, G.M.; et al. SARS-CoV-2 Spike Protein Induces TLR4-Mediated Long-Term Cognitive Dysfunction Recapitulating Post-COVID-19 Syndrome in Mice. *Cell Rep.* **2023**, *42*, 112189, doi:10.1016/j.celrep.2023.112189.
281. Monje, M.; Iwasaki, A. The Neurobiology of Long COVID. *Neuron* **2022**, *110*, 3484–3496, doi:10.1016/j.neuron.2022.10.006.
282. Mentor, G.; Farrar, D.S.; Di Chiara, C.; Dufour, M.-S.K.; Valois, S.; Taillefer, S.; Drouin, O.; Renaud, C.; Kakkar, F. The Effect of Age and Comorbidities: Children vs. Adults in Their Response to SARS-CoV-2 Infection. *Viruses* **2024**, *16*, doi:10.3390/v16050801.
283. Sievers, B.L.; Cheng, M.T.K.; Csiba, K.; Meng, B.; Gupta, R.K. SARS-CoV-2 and Innate Immunity: The Good, the Bad, and the "Goldilocks." *Cell. Mol. Immunol.* **2024**, *21*, 171–183, doi:10.1038/s41423-023-01104-y.
284. Minkoff, J.M.; tenOever, B. Innate Immune Evasion Strategies of SARS-CoV-2. *Nat. Rev. Microbiol.* **2023**, *21*, 178–194, doi:10.1038/s41579-022-00839-1.
285. Zanza, C.; Romenskaya, T.; Manetti, A.C.; Franceschi, F.; La Russa, R.; Bertozzi, G.; Maiese, A.; Savioli, G.; Volonnino, G.; Longhitano, Y. Cytokine Storm in COVID-19: Immunopathogenesis and Therapy. *Medicina (Kaunas).* **2022**, *58*, doi:10.3390/medicina58020144.
286. Zhao, N.; Di, B.; Xu, L.-L. The NLRP3 Inflammasome and COVID-19: Activation, Pathogenesis and Therapeutic Strategies. *Cytokine Growth Factor Rev.* **2021**, *61*, 2–15, doi:10.1016/j.cytogfr.2021.06.002.
287. Zaim, S.; Chong, J.H.; Sankaranarayanan, V.; Harky, A. COVID-19 and Multiorgan Response. *Curr. Probl. Cardiol.* **2020**, *45*, 100618, doi:10.1016/j.cpcardiol.2020.100618.
288. Lazzaroni, M.G.; Piantoni, S.; Masneri, S.; Garrafa, E.; Martini, G.; Tincani, A.; Andreoli, L.; Franceschini, F. Coagulation Dysfunction in COVID-19: The Interplay between Inflammation, Viral Infection and the Coagulation System. *Blood Rev.* **2021**, *46*, 100745, doi:10.1016/j.blre.2020.100745.
289. Eaton-Fitch, N.; Rudd, P.; Er, T.; Hool, L.; Herrero, L.; Marshall-Gradisnik, S. Immune Exhaustion in ME/CFS and Long COVID. *JCI insight* **2024**, *9*, doi:10.1172/jci.insight.183810.