University of Cyprus
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Human immune responses upon SARS-CoV-2 infection-inflammation and cytokine storm

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that emerged in December 2019 in the city of Wuhan, China, causing the COVID-19 pandemic of acute respiratory disease. Since its emergence, SARS-CoV-2 has infected over 639 million people and caused more than 6 million deaths worldwide, highlighting the urgent need to develop effective antiviral therapeutics and prevention strategies. SARS-CoV-2 is an enveloped virus belonging to the genus *Betacoronavirus*, with a large positive-sense single-stranded RNA (+ssRNA) genome of about 30 kilobases (kb) in length. The viral genome encodes a set of structural proteins (spike glycoprotein, membrane protein, nucleocapsid protein, and envelope protein), non-structural proteins (NSPs), and accessory proteins, which participate in host recognition and entry, genome replication and transcription, viral assembly, and release, as well as in host immune surveillance evasion. The effective host immune response against SARS-CoV-2 is mounted by both the innate and adaptive arms of immunity, and is essential for controlling and resolving the viral infection. However, multiple studies have shown that SARS-CoV-2 suppresses normal antiviral immune responses, leading to an impaired immune system and uncontrolled inflammatory responses in patients with severe COVID-19. Severe COVID-19 is associated with hyperactivation of innate immune cells, overproduction and uncontrolled release of proinflammatory cytokines, a condition known as "cytokine storm", dysregulated interferon (IFN) responses, reduced T cell numbers, lymphocyte exhaustion as well as exacerbated antibody responses. Based on the current scientific knowledge, this review focuses on host immune responses against SARS-CoV-2 infection, including the contribution of a dysfunctional immune system to disease progression and mortality. An improved understanding of the mechanisms underlying immune abnormalities in severe COVID-19 cases may increase our ability to treat and prevent coronavirus (CoV) infections in this pandemic and beyond.

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SEMINAR ANNOUNCEMENT

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Andriani Syrimi

Thesis Supervisor: Special Teaching Staff, Dr. Annita Charalambous

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1. INTRODUCTION

Coronaviruses (CoVs) are a highly diverse family of enveloped, positive-stranded RNA viruses with remarkably large genomes of ~30 kilobases (kb), the largest of all RNA viruses (Fehr and Perlman, 2015). They have been detected in a wide range of animals and humans, causing principally respiratory and gastrointestinal infections. Coronaviruses belong to the Coronaviridae subfamily Orthocoronavirinae, which is further divided into four genera based on genomic and phylogenetic analysis: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus* (Woo et al., 2012, Fung and Liu, 2019). Currently, there are seven strains of alpha- and betacoronaviruses able to cause human illness (Abdelrahman et al., 2020). Among these, two highly pathogenic coronaviruses with zoonotic origin have emerged in the human population over the past twenty years, causing large-scale outbreaks and severe human respiratory diseases (Cui et al., 2019): 1) the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in Guangdong, Southern China, 2002 (Kuiken et al., 2003) and 2) the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabia, 2012 (Zaki et al., 2012).

In late December 2019, several health facilities in the city of Wuhan, Hubei Province, China, reported a series of unusual pneumonia cases, and the causative pathogen was isolated and identified as a novel *Betacoronavirus*, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhu et al., 2020). The World Health Organization (WHO) officially named the infectious disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), which was declared a worldwide pandemic on March 11, 2020 (Hu et al., 2021). Although less deadly than SARS and MERS, SARS-CoV-2 is spreading more rapidly with devasting consequences in global public health and economy, highlighting the urgent need to develop effective antiviral therapeutics and prevention strategies (Wang et al., 2020). The novel COVID-19 disease is the third wave of coronavirus outbreak to arise in the twenty-first century, following SARS and MERS, indicating that coronaviruses continue to pose a major threat to public health (Zhong et al., 2003, Zaki et al., 2012, Wu et al., 2020).

Of the initial documented COVID-19 patients, most cases had direct exposure to a large seafood wholesale market located in downtown Wuhan, that also traded in live wild animals, suggesting that the virus likely originated in zoonotic transmissions from animal hosts to humans (Tay et al., 2020, Jiang et al., 2020). Later, more patients who had no association with

this market were reported. Several familial clusters of viral pneumonia associated with SARS-CoV-2 were identified, and nosocomial infections also occurred in healthcare facilities, providing clear evidence that SARS-CoV-2 is capable of human-to-human transmission (Chan et al., 2020, Deng and Peng, 2020, Chen et al., 2020). Like other respiratory coronaviruses, SARS-CoV-2 is transmitted among the human population primarily via respiratory droplets of infected persons and direct physical contact as well as via contaminated surfaces or objects (Kumar and Al Khodor, 2020). It is now well established that SARS-CoV-2 interaction with the host immune system, typically with other risk factors, underlies the diverse clinical manifestations of COVID-19 and determines the course of disease progression (Brodin, 2021). Although in some cases the infection is asymptomatic, the majority of young people infected with SARS-CoV-2 develop a mild-to-moderate respiratory disease (non-pneumonia or mild pneumonia), experiencing common-cold symptoms that include fever, cough, fatigue, and myalgia, which resolve within a few days (Harrison et al., 2020). In contrast to the mild illness, some individuals exhibit severe pneumonia with shortness of breath and hypoxemia that can progress to potentially fatal systemic lung inflammation, cytokine storm, acute respiratory distress syndrome (ARDS), cardiac and renal injury, and multiorgan dysfunction, requiring hospital admission in an intensive care unit (ICU) (Wang et al., 2020, Small et al., 2021). Older people and patients with underlying medical comorbidities (for example, diabetes, hypertensive disease, and obesity) appear to be at a higher risk of severe illness, respiratory failure, and death (Richardson et al., 2020, Barman et al., 2021).

1.1 The genome organization of SARS-CoV-2 and its coded proteins

The SARS-CoV-2 genome is comprised of a non-segmented, large positive-sense single-stranded RNA (+ssRNA) with a length of ~30 kb, that acts as a molecular message enabling the production of other viral elements (Wu et al., 2022). As a novel *Betacoronavirus*, SARS-CoV-2 has been reported to share about 79% similarity in genome sequence with previously known SARS-CoV and about 50% with MERS-CoV (Lu et al., 2020). The viral genome contains a 5′-cap structure, a 3′-poly-A tail, 14 open reading frames (ORFs), and encodes about 29 viral proteins (Chen et al., 2020, Yang and Rao, 2021). In SARS-CoV-2 the 5′-proximal two-thirds of the genome contains the replicase gene, which encodes two large polyproteins, pp1a and pp1ab, synthesized from two open reading frames, ORF1a and ORF1b (Yadav et al., 2021) (see **Figure 1**). The two viral replicase polyproteins undergo a series of proteolytic cleavages by virus-encoding proteases, including the main protease (M^{pro}), also known as 3-chymotrypsin-like cysteine protease ($3CL^{pro}$), and papain-like protease (PL^{pro}), to produce

sixteen mature non-structural proteins (NSPs) (Chen et al., 2020). These NSPs play a key role in viral RNA replication and transcription as well as in host immune surveillance evasion (Yang and Rao, 2021, Thomas, 2021). The remaining one-third of the viral genomic region near the 3′ terminus consists of overlapping ORFs, encoding four major structural proteins, involving spike glycoprotein (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, which are responsible for the functional and structural aspects of the virus (Wu et al., 2022). Additionally, a series of accessory genes, which encode several accessory proteins, are distributed among the structural genes (Chan et al., 2020). Coronavirus accessory proteins are involved in modulating viral infection and often have immunoevasive activities (Yang and Rao, 2021, Lamers and Haagmans, 2022).

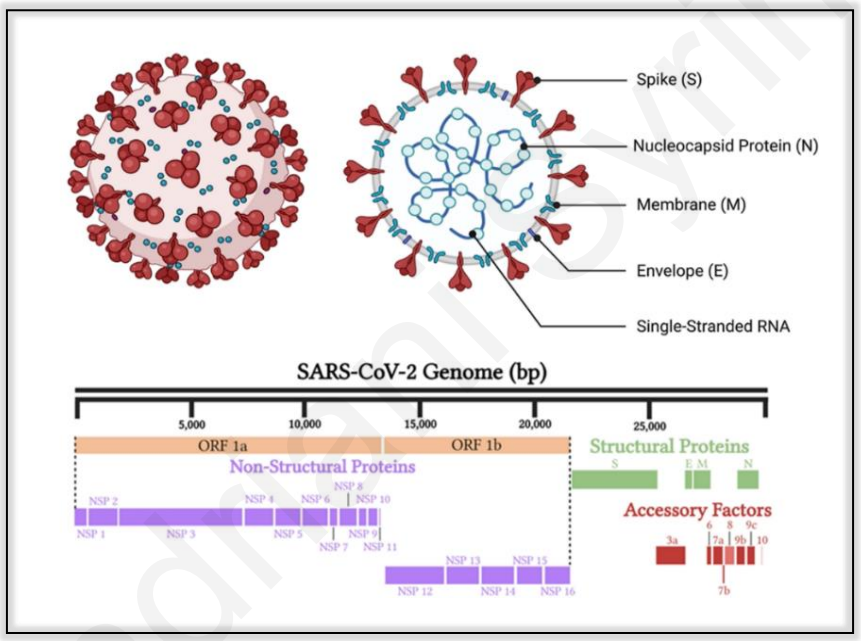

Figure 1. *Structural features of SARS-CoV-2 and genomic organization (Generated by Jamison et al., 2022).*

The structural proteins together with a lipid-bilayer membrane derived from the host cell, form a spherical enveloped virion that delivers viral genomic RNA into the cell (Ke et al., 2020). Among four structural proteins, S, M, and E are embedded in virion surface membranes (Wu et al., 2022). SARS-CoV-2 is decorated with long, petal-shaped surface projections, composed of trimers of the spike glycoprotein, giving the virus its crown-like appearance (hence, "corona") (Kumar et al., 2021). This heavily glycosylated protein belongs to the so-called class I viral fusion proteins and mediates major entry steps, including the attachment of the virus to host cell-surface receptors and viral cell membrane fusion (Belouzard et al., 2012). The M protein is the most abundant structural protein on the viral surface responsible for defining the

size and shape of the viral envelope (Masters, 2006, Neuman et al., 2011). It possesses a short-length N-terminal glycosylated ectodomain followed by a triple-membrane-spanning domain and a longer C-terminal domain inside the viral envelope. The M glycoprotein interacts with other structural proteins of the virus, including both N and S proteins, to facilitate the assembly of new infectious virus particles within the host cells (Fu et al., 2021). The SARS-CoV-2 E protein is the smallest of the major transmembrane structural proteins which appears to be a critical multifunctional protein (Yadav et al., 2021). As a viral ion channel viroporin, E protein provides a platform for viral assembly and budding from infected cells but also participates in virion morphogenesis and pathogenicity (Mandala et al., 2020, Schoeman and Fielding, 2019, Yan et al., 2022). During viral replication, it is predominantly localized at the site of intracellular trafficking and more specifically at the endoplasmic reticulum (ER) and the Golgi body membranes (Yang and Rao, 2021). Within the lumen of the virion, the phosphoprotein N binds to viral genomic RNA forming a long, flexible, helical nucleocapsid (Arya et al., 2021). In addition to being involved in viral genome RNA packaging, the N protein inhibits a lot of the host cells' defense mechanisms and promotes viral RNA synthesis and virion assembly (Satarker and Nampoothiri, 2020, Sheikh et al., 2020). It is highly immunogenic and is produced in high abundance during infection, and thus comprises a potential target for vaccine development (Bai et al., 2021).

1.2 SARS-CoV-2 receptor ACE2

The initial steps of SARS-CoV-2 infection process involve the interaction of the coronavirus surface spike protein with the cellular entry receptors and the following membrane fusion (V'kovski et al., 2021). The SARS-CoV-2 homotrimeric S glycoprotein, protruding from the viral lipid envelope as an extensive crown, binds to the host cell surface receptor angiotensin-converting enzyme 2 (ACE2), to facilitate coronavirus entry into the target cells (Tortorici and Veesler, 2019, Zhou et al., 2020, Hoffmann et al., 2020). ACE2, the first human homologue of angiotensin-converting enzyme (ACE), is a zing-containing carboxypeptidase composed of 805 amino acids and characterized by an N-terminal catalytic peptidase domain, a single metalloproteinase active site and a C-terminal membrane-anchor collectrin-like domain with a cytoplasmic tail on the intracellular side (Tipnis et al., 2000, Donoghue et al., 2000). Although ACE2 is hijacked by some coronaviruses, its primary role in normal physiology is to regulate blood pressure and cardiac function as well as to maintain electrolyte and fluid homeostasis, through negatively modulating the renin-angiotensin-aldosterone system (RAAS) (Verdecchia et al., 2020, Hoffmann et al., 2020, Zhang et al., 2021). Briefly, the classical RAAS cascade

starts with the conversion of the serum globulin angiotensinogen, produced by the liver, to angiotensin I (Ang I) decapeptide through the action of renal renin. Angiotensin I is then hydrolyzed to the octapeptide angiotensin II (Ang II), a potent vasoconstrictor, growth modulator, and stimulant of aldosterone release, by endothelial ACE, a process that occurs predominantly in lung tissue (Putnam et al., 2012, Verdecchia et al., 2020). Ang II binds to the angiotensin type-1 receptor (AT_1R) leading to increased blood pressure via increased renal water, sodium retention, and vascular constriction. Ang II binding to AT_1R also stimulates proinflammatory chemokines and endothelial dysfunction to promote inflammation. Integral to the RAAS signaling pathway, ACE2 catalyzes with high efficiency the conversion of angiotensin I and angiotensin II, synthesized by renin and ACE, into the angiotensin 1–9 and angiotensin 1–7 peptides, respectively, thereby inhibiting vasoconstriction, cell proliferation, and inflammation (Medina-Enríquez et al., 2020, Zamorano Cuervo and Grandvaux, 2020). Although ACE2 functions as a counter-regulator of the RAAS pathway, in SARS-CoV-2 infection the interaction of viral spike protein with the ACE2 receptor results in the downregulation of ACE2 expression followed by a subsequent increase in circulating Ang II levels (Kuba et al., 2005). Therefore, the reduction in ACE2 function creates a dysregulation with overactivation of the RAAS system, increasing vascular permeability and leading to lung oedema and impaired lung function (Gheblawi et al., 2020).

In the lower respiratory tract, ACE2 expression is relatively limited to type II alveolar epithelial cells, but it is expressed at higher levels in the upper bronchial epithelial cells and ciliated cells in the nasal mucosa (Sungnak et al., 2020, Hou et al., 2020, Ahn et al., 2021). Despite the respiratory route being dominant in SARS-CoV-2 infection, expression of the ACE2 receptor is also found in many extrapulmonary tissues, including heart muscle, kidney, small intestine, thyroid gland, testes, and brain, allowing the virus to infect the human body in various ways (Ye et al., 2004, Doobay et al., 2007, Wang et al., 2020). In addition to ACE2, other host entry factors involving several C-type lectin receptors (e.g., DCL-SIGN, L-SIGN), neuropilin-1 (NRP1), CD147, and toll-like receptors (TLRs) have been suggested to serve as alternative SARS-CoV-2 receptors capable of triggering viral attachment and entry (Trbojević-Akmačić et al., 2021, Jackson et al., 2022).

1.3 SARS-CoV-2 entry process

Like in SARS-CoV and other coronaviruses, SARS-CoV-2 requires proteolytic processing of the spike protein by host cell-derived proteases to activate the potential infection routes

(Jackson et al., 2022). Depending on the availability of cellular proteases, SARS-CoV-2 can enter and infect host cells using two distinct entry pathways, either by direct fusion of the viral envelope with the host cell plasma membrane or by receptor-mediated endocytosis (see **Figure 2**). During biosynthesis and posttranslational maturation in the infected cell, the transmembrane S protein is cleaved by furin or furin-like proteases in the Golgi-apparatus into two functionally distinct parts, a receptor-binding fragment (S1) and a membrane fusion fragment (S2) (Duan et al., 2020, Wu et al., 2022). This step is a prerequisite for the activation of its membrane-fusion capacity. After furin-mediated cleavage at the S1–S2 boundary, the S1 and S2 subunits remain non-covalently bound in a metastable prefusion conformation (Walls et al., 2020). The surface-exposed S1 subunit consists of an N-terminal domain (S1-NTD) and a receptor-binding domain (RBD) that specifically recognizes the ACE2 receptor on the host cellular membrane, thereby determining virus cell tropism and pathogenicity. The SARS-CoV-2 RBD contains a receptor-binding motif (RBM), and the C-terminal domains (CTDs) composed of CTD1 and CTD2 (Zhang et al., 2021). The interface between the spike RBD and ACE2 is formed primarily by a gently concave outer surface of the extended RBM and the N-terminal peptidase domain of the receptor (Lan et al., 2020). Importantly, RBD can adopt two different conformational states, either a closed 'down' state for immune evasion or an open 'up' state for receptor binding (Shang et al., 2020, Wrapp et al., 2020). To engage the ACE2 receptor, RBD undergoes a conformational transition from the down to the up conformation, exposing the receptor-binding motif, and thus facilitating ACE2 interaction. The membrane-anchored S2 subunit is divided into four multi-structural regions: a hydrophobic fusion peptide, two heptad repeats (HR1 and HR2), and a transmembrane segment. Depending on the entry pathway taken by SARS-CoV-2, the spike protein is further cleaved at a second site internal to the S2 subunit, the S′ site, by the transmembrane serine protease 2 (TMPRSS2) on the cell surface, or the endosomal cysteine proteases cathepsins B and L (acidic pH-dependent endocytosis), following ACE2 engagement by the virus, to expose the internal fusion peptide for membrane fusion (Gierer et al., 2013, Ou et al., 2020, Hoffmann et al., 2020). Interaction of RBD with SARS-CoV-2 cell entry receptor along with the two proteolytic cleavage events initiate a cascade of dramatic conformational changes in the metastable prefusion S2, accompanied by complete dissociation of S1 from the spike. The two heptad repeat regions of the S2 subunit, HR1 and HR2, gradually approach each other and constitute a tightly bound six-helix bundle (6-HB), allowing the fusogenic transition to a stable rigid postfusion structure that is essential for fusion of the viral envelope with the plasma membrane or the endosomal

membranes (Fan et al., 2020). This structural rearrangement brings viral and host cell membranes in proximity, effectively leading to fusion pore formation, which allows the viral positive-sense, single-stranded RNA genome to reach the cytoplasm of host cells for uncoating and replication. Once viral RNA is released into the cytoplasm, host ribosomes are hijacked to translate RNA and produce viral proteins as well as genomic RNA and multiple subgenomic mRNAs. The newly synthesized genomic RNA and the translated structural proteins are assembled in the endoplasmic reticulum and Golgi body, to form mature progeny virions. Finally, progeny virions are transported to the cell surface in large, smooth-walled vesicles and released from the infected cell by exocytosis, to complete the life cycle and initiate another round of infection (Harrison, et al., 2020).

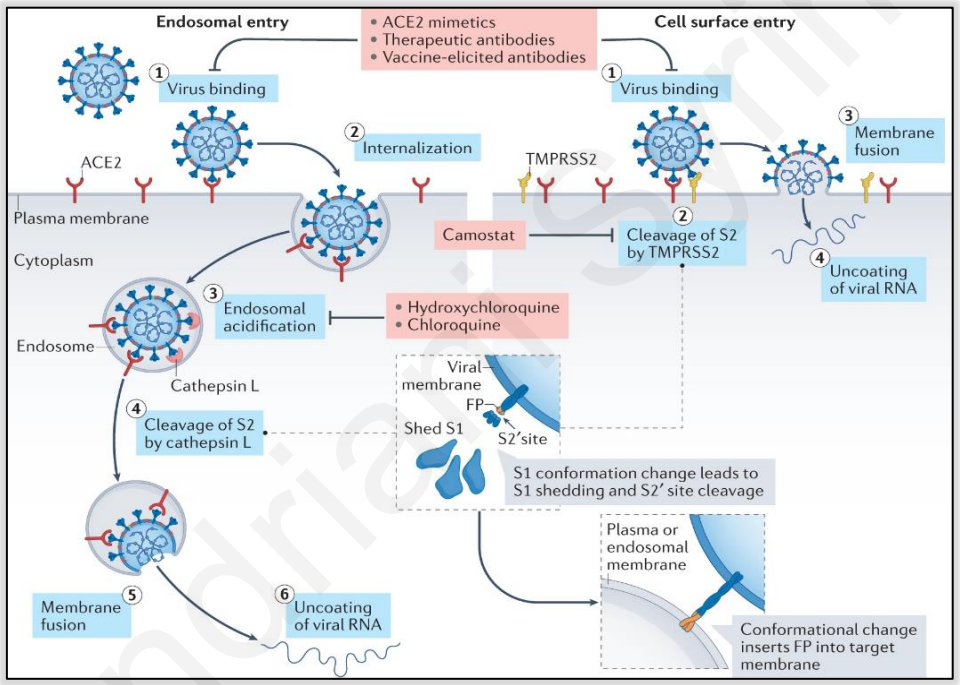

Figure 2. *Two distinct pathways for SARS-CoV-2 entry into the target cells (Generated by Jackson et al., 2022).*

Human immune responses to pathogen invasion, including both innate and adaptive immunity, are essential for blocking viral infection and eliminating infected cells (Li et al., 2020). On binding to target cells in the respiratory tract, SARS-CoV-2 causes the activation and recruitment of immune cells at the site of infection, subsequently releasing various cytokines, chemokines, and other alarmins and priming adaptive immunity to orchestrate an effective antiviral response. In most cases, the host immunoregulatory system is capable of resolving the infection following this process (Tay et al., 2020). However, dysregulation of the different mechanisms of innate and adaptive immunity can result in further accumulation of immune

cells in the lungs, causing a massive cytokine expression - "cytokine storm" -, which eventually damages the lung infrastructure (Yang et al., 2021). The hyperinflammation triggered by SARS-CoV-2 inflicts multi-organ injury leading to organ failure and death. Coronaviruses including SARS-CoV-2 have evolved several strategies to evade host antiviral defense programs, which results in successful viral transmission and adaptation to the human host (Kasuga et al., 2021). The purpose of this work is to summarize the current knowledge of the underlying human immune responses against SARS-CoV-2 infection, highlighting the contribution of dysregulated host immune system to disease progression, with particular focus on the COVID-19 cytokine storm. A comprehensive understanding of immunity and its regulation in response to SARS-CoV-2 infection will offer important insights into the identification of new therapeutic targets for COVID-19 and prevention of viral spread.

2. OVERVIEW

2.1 Innate immune response to SARS-CoV-2

2.1.1 Host innate immune sensors

The first response to a viral infection is the rapid-onset innate immune response. This is the primary line of host defense against non-specific infectious challenges, including SARS-CoV-2 (Diamond and Kanneganti, 2022). Innate immune cells, including macrophages, monocytes, dendritic cells, and natural killer (NK) cells, are armed with an arsenal of germline-encoded pattern recognition receptors (PRRs) that have evolved to recognize unique molecular structures on the surface of foreign pathogens known as pathogen-associated molecular patterns (PAMPs), as well as host molecules associated with disturbance of homeostasis referred to as damage-associated molecular patterns (DAMPs) (Kanneganti, 2020). Different host innate immune receptors have been reported to be involved in sensing SARS-CoV-2 infection, including the Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). Once activated, these and other receptors subsequently activate complex intracellular signaling networks, leading to the synthesis of a variety of inflammatory cytokines and chemokines as well as interferons (IFNs) that promote viral clearance, mediate the induction of innate immune responses, and ultimately shape adaptive immunity.

2.1.2 Sensing of SARS-CoV-2 invasion by TLRs

Upon infection with SARS-CoV-2, an innate immune response is activated through the phylogenetically preserved TLR family. The understanding of mechanisms used by the innate immune system to sense microbial invasion has been greatly advanced through the discovery and characterization of TLRs. TLRs comprise a family of type I transmembrane receptors, which recognize specific molecular patterns that are present in microbial components (Gao et al., 2017). To date, 10 members of the TLR family have been discovered in humans, of which TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are expressed on cell surfaces and recognize lipid and protein ligands derived from invading pathogens (Mahla, 2013, Gay et al., 2014). In contrast, TLR3, TLR7, TLR8, and TLR9 are expressed exclusively in endolysosomal compartments detecting distinct forms of viral nucleic acids (Sellge and Kufer, 2015). Upon stimulation, TLRs activate specific downstream signaling pathways by recruiting key adapter molecules, the myeloid differentiation primary response protein 88 (MyD88), and TIR domain-containing adapter protein inducing IFNβ (TRIF), providing specific immunological responses tailored to the infecting microbes (Lim et al., 2016). The signaling adapter MyD88 utilized by

all TLRs (except for TLR3), activates the nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPK) signaling pathways, triggering inflammatory cytokine production such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), and IL-12. On the other hand, the TRIF-dependent pathway utilized by TLR3 and TLR4 is associated with the stimulation of interferon (IFN)-regulatory factors (IRFs) (Kawai and Akira, 2011).

The work of Zheng et al. revealed that TLR2 was positively correlated with COVID-19 disease severity and required for SARS-CoV-2-mediated induction of inflammatory responses and cytokine production through sensing the envelope protein of SARS-CoV-2 as its ligand (Zheng et al., 2021). The SARS-CoV-2 E protein had the potential to induce TLR2-dependent lung inflammation and damage in vivo, as the amount of IL-6 was decreased in TLR2$^{-/-}$ mice upon administration of the E protein. Blocking TLR2 signaling by the TLR2-specific inhibitor oxidized PAPC (oxPAPC) significantly decreased the secretion of inflammatory cytokines and chemokines, such as IL-6, TNF-α, IFN-γ, CXCL10, and MCP-1 in SARS-CoV-2 infected K18-human ACE2 (hACE2) transgenic mice (see **Figure 3a**) and provided protection against SARS-CoV-2 mortality (see **Figure 3b**), suggesting an essential role of this innate immune receptor in viral pathogenesis.

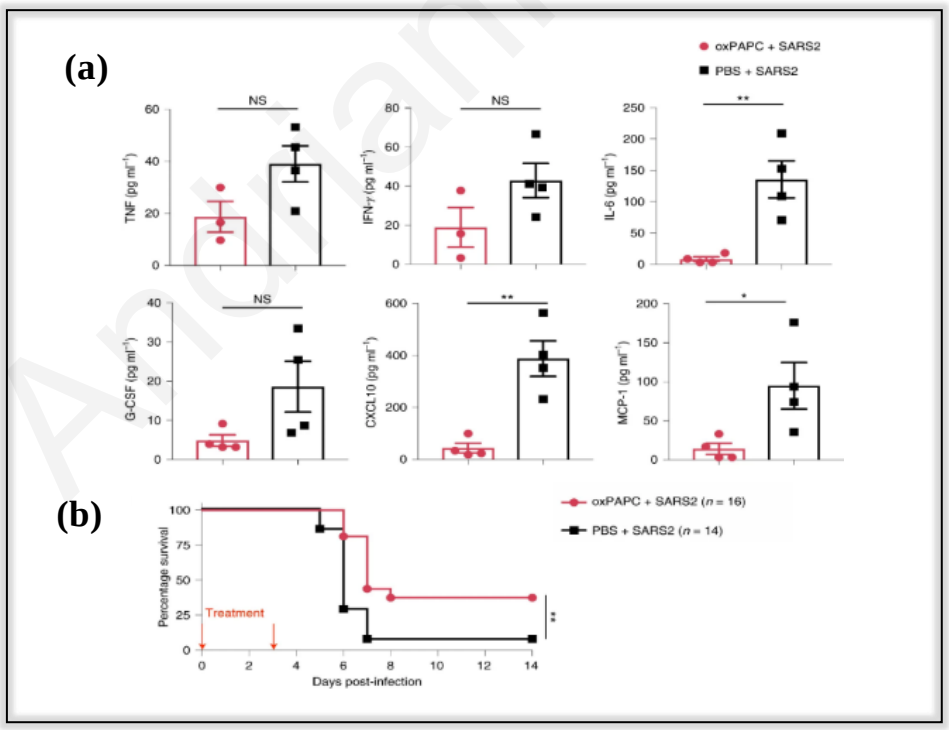

Figure 3. (a) *Decreased cytokine and chemokine levels in SARS-CoV-2-infected mice treated with the TLR2-specific inhibitor oxPAPC.* ***(b)*** *Increased survival of the SARS-CoV-2-infected mice after TLR2 inhibition (Generated by Zheng et al., 2021).*

Additionally, an independent single-cell-based computational analysis aimed at predicting protein modulators of the dysregulated inflammatory response during SARS-CoV-2 infection also suggested that TLR2 is involved in innate immune activation (Jung et al., 2021).

In contrast to these results, another group identified the SARS-CoV-2 spike glycoprotein, but not the envelope protein, as a driver of TLR2 activation (TLR2 forms heterodimers with TLR1 or TLR6), leading to the subsequent activation of the NF-κB signaling pathway and induction of cytokines and other inflammatory molecules in innate immune cells (monocytes and macrophages) and human lung epithelial cells (Khan et al., 2021). Upon stimulation of TLR2-deficient mouse bone marrow-derived macrophages (mBMDMs) with SARS-CoV-2 S1 and S2 proteins, there was no activation of the NF-κB pathway (see **Figure 4a**). Consistently, administration of S1 and S2 proteins into wild-type (WT) mice resulted in increased levels of the inflammatory cytokines IL-6, IL-1β, and TNFα, whereas no such induction was observed in TLR2-deficient mice (see **Figure 4b**).

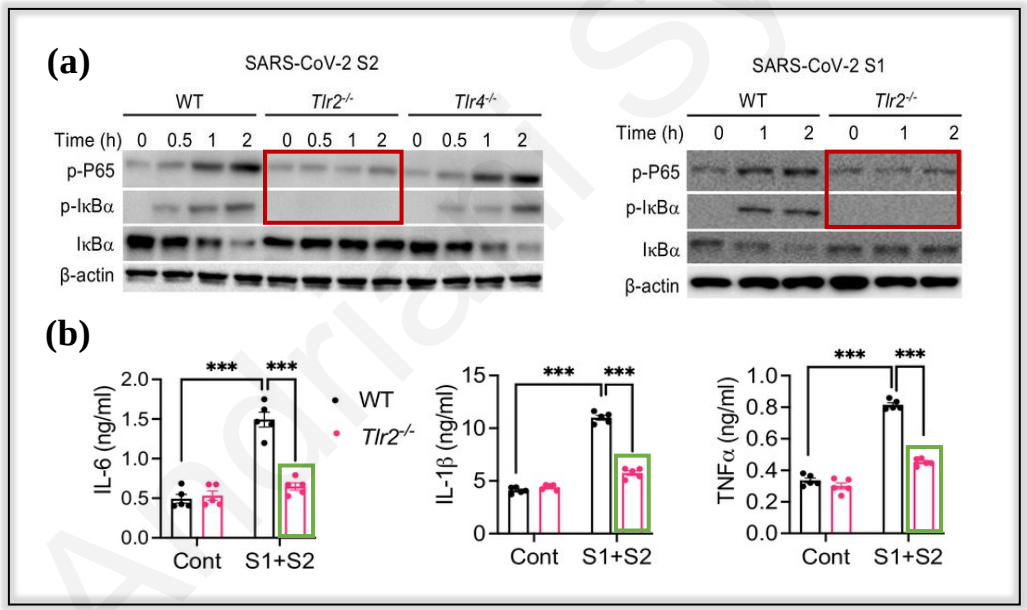

Figure 4. (a) *Defective activation of the NF-κB pathway in Tlr2$^{-/-}$ macrophages treated with SARS-CoV-2 S1 and S2 proteins.* ***(b)*** *Decreased concentration of IL-6, IL-1β, and TNFα in Tlr2$^{-/-}$ mice after administration of SARS-CoV-2 S1 and S2 proteins (Generated by Khan et al., 2021).*

A previous in silico study also suggested a possible interaction between the S protein of SARS-CoV-2 and certain members of human cell surface TLRs, including TLR4 (Choudhury and Mukherjee, 2020). Using a molecular docking-based computational approach, the authors found that the innate immune receptor TLR4 possessed a strong binding affinity to the SARS-

CoV-2 S protein following TLR6 and TLR1, indicating a potential role for TLR4 in SARS-CoV-2 recognition and induction of inflammatory responses (see **Figure 5**).

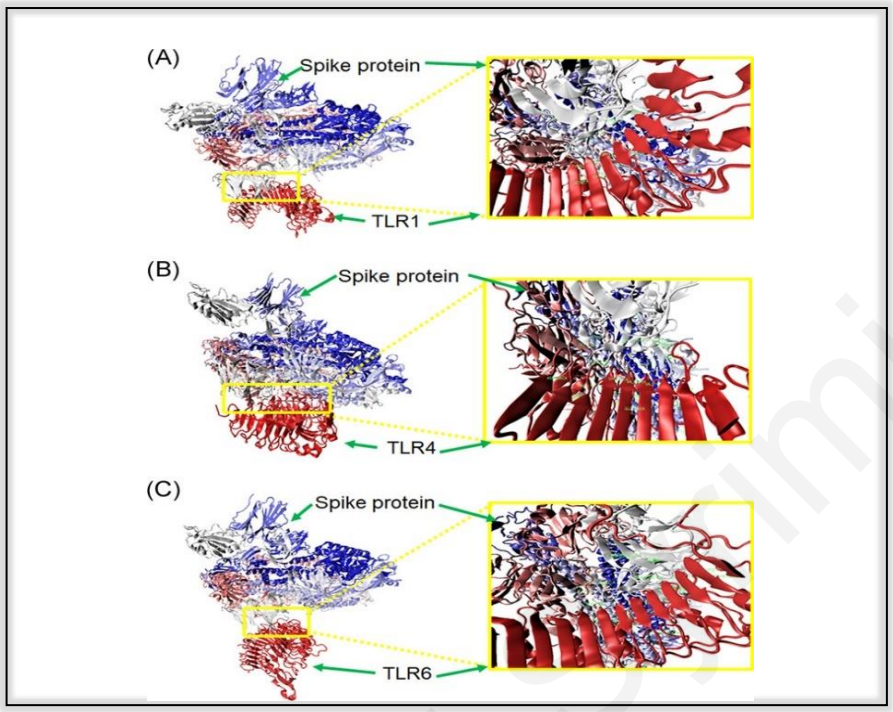

Figure 5. *Molecular docking showing interaction of SARS-CoV-2 spike protein with the extracellular domains of* ***(A)*** *TLR1,* ***(B)*** *TLR4, and* ***(C)*** *TLR6 (Generated by Choudhury and Mukherjee, 2020).*

In support of this hypothesis, Shirato and Kizaki showed that the SARS-CoV-2 spike protein S1 subunit activated TLR4 signaling to induce proinflammatory cytokine production as well as the activation of NF-κB and stress-activated MAPK signaling pathways in murine and human macrophages. S1-induced proinflammatory responses in macrophages were significantly suppressed following treatment with the TLR4 antagonist LPS-RS or by RNAi targeting TLR4 (Shirato and Kizaki, 2021). On the other hand, a separate study showed that only the trimeric spike protein was capable of interacting with TLR4 and activating immune responses in macrophages (Zhao et al., 2021).

In addition, results of rapid clinical whole exome sequencing in young male patients with severe COVID-19 from two unrelated families revealed the presence of rare putative loss-of-function variants of the X-chromosomal TLR7 that were linked to transcriptional downregulation of type I IFN signaling in peripheral blood mononuclear cells (PBMCs) from patients, as indicated by significantly reduced mRNA expression of the genes IRF7, IFNB1, and ISG15 (van der Made et al., 2020). These findings suggest a key role for TLR7 in COVID-19 pathogenesis. Using a candidate gene approach, Zhang et al. identified autosomal-recessive

(AR) or autosomal-dominant (AD) deficiencies of genes involved in the regulation of type I and III IFN responses in patients with life-threatening COVID-19 pneumonia (Zhang et al., 2020). Plasmacytoid dendritic cells (pDCs) isolated from patients with interferon regulatory factor 7 (IRF7) deficiency had impaired production of type I IFN on infection with SARS-CoV-2, while IRF7 deficient fibroblasts were vulnerable to SARS-CoV-2 in vitro.

2.1.3 Sensing of SARS-CoV-2 invasion by RLRs and IFN signaling

Upon SARS-CoV-2 infection, the invaded single-stranded RNA or other RNA compositions, and replicative intermediates of the virus can be sensed by innate immune cells via ubiquitously expressed RLRs, which are primarily localized in the cytoplasm (Yin et al., 2021, Yang et al., 2021, Rebendenne et al., 2021). The RLR protein family is composed of three members: RIG-I, melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) (Rehwinkel and Gack, 2020). Structurally, all RLRs possess a central helicase domain and a C-terminal domain (CTD) that work synergistically to detect immunostimulatory RNAs. The RNA sensors RIG-I and MDA5 also contain two tandem caspase activation recruitment domains (CARDs) in their N-terminal regions, which mediate downstream signal transduction. RIG-I and MDA5 are the most well-studied RLRs and have been shown to play an important role in antiviral defense and regulation of IFN pathways (Kato et al., 2006, Gitlin et al., 2006). Activated RIG-I and MDA5 translocate to the mitochondria, where they liberate CARDs to bind to the mitochondrial antiviral signaling protein (MAVS) also termed as VISA/IPS-1/Cardif), which serves as the essential adapter protein for RLR-mediated signaling. This complex formation activates the two IKK-related kinases, TANK-binding kinase (TBK)1, and IκB kinase (IKK), as well as the TNF receptor-associated factor (TRAF)3, ultimately resulting in the phosphorylation of interferon regulatory factor 3/7 (IRF3/7), which translocates to the nucleus and transiently induces transcription of the genes encoding type I and type III IFNs (Goubau et al., 2013). Secreted IFNs signal in a paracrine and autocrine manner, triggering the expression of hundreds of interferon-stimulated genes (ISGs) that endow host cells with antiviral abilities. Additionally, these cytoplasmic nucleic acid sensors have the capacity to induce the expression of inflammatory cytokines.

The viral RNA sensors MDA5 and LGP2 were identified as the predominant receptors involved in innate immune sensing of SARS-CoV-2 infection (Yin et al., 2021). Targeted knockdown or knockout of MDA5, LGP2, and MAVS (antiviral adapter molecule) genes in human lung airway epithelial or Calu-3 cells drastically reduced type I IFN expression during SARS-CoV-2 infection, suggesting a dominant role of both MDA5 and LGP2 in antiviral type I IFN

induction in response to SARS-CoV-2 infection (see **Figure 6**) (Yin et al., 2021, Yang et al., 2021, Rebendenne et al., 2021).

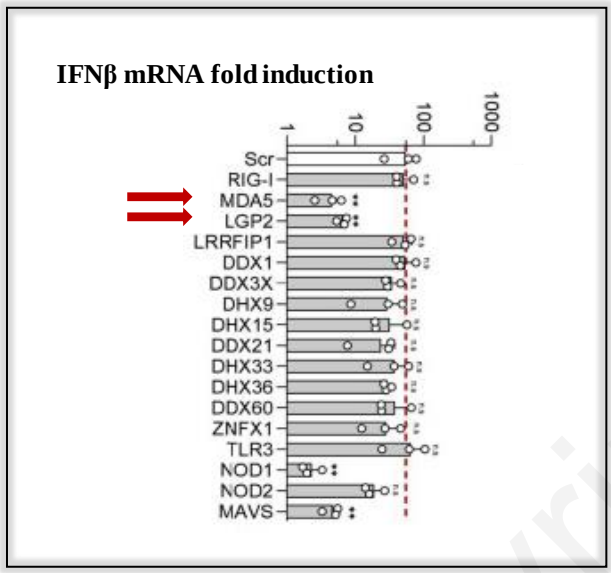

Figure 6. *Decreased IFNβ expression in MDA5- and LGP2-knockdown Calu-3 cells (Generated by Yin et al., 2021).*

On the other hand, RIG-I produced contradictory results. In one study small interfering RNA (siRNA)-mediated RIG-I depletion markedly decreased IFNβ expression in Calu-3 cells infected with SARS-CoV-2 (see **Figure 7a**) (Thorne et al., 2021). In contrast, another study demonstrated that silencing the gene encoding RIG-I had no effect on IFN production in response to SARS-CoV-2 infection in Calu-3 lung epithelial cells, and its deletion by the genome editing tool CRISPR-Cas9 targeting in Calu-3 cells also did not impact the amounts of type I and type III IFNs expressed during SARS-CoV-2 infection (see **Figure 7b**) (Yin et al., 2021, Rebendenne et al., 2021).

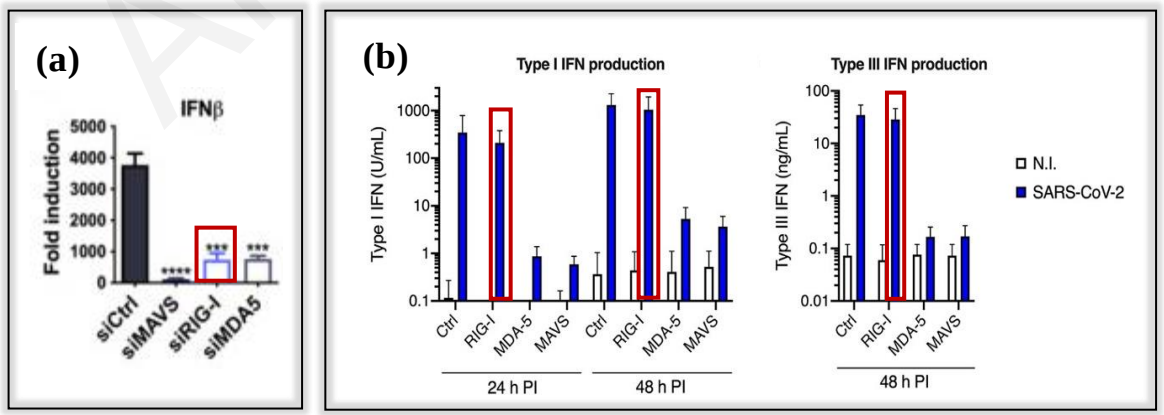

Figure 7. Contradictory results with RIG-I. (a) *Decreased IFNβ expression in siRNA-RIG-I Calu-3 cells infected with SARS-CoV-2 (Generated by Thorne et al., 2021).* ***(b)*** *Increased concentrations of type I and III IFNs in RIG-I-knockout Calu-3 cells infected with SARS-CoV-2 (Generated by Rebendenne et al., 2021).*

2.1.4 Impaired type I IFN responses in COVID-19

The type I IFN responses play a crucial role in the defense against viral infections promoting viral clearance and influencing the development of innate and adaptive immune responses (McNab et al., 2015). However, similar to other highly pathogenic and potentially lethal coronaviruses, SARS-CoV-2 has evolved multiple strategies to hamper host antiviral immune responses by antagonizing the IFN system, especially through its encoded proteins (Kim and Shin, 2021). Accumulating evidence reported that the protective type I IFN responses were dysregulated in severe cases of COVID-19 (Blanco-Melo et al., 2020, Hadjadj et al., 2020, Galani et al., 2021). Hadjadj et al. identified a highly impaired type I IFN response in the peripheral blood of severe or critical COVID-19 patients, with no detectable circulating IFNβ and low IFNα production and activity, suggesting that type I IFN deficiency could be an immunological characteristic of severe COVID-19 and could identify a high-risk population (see **Figure 8a**) (Hadjadj et al., 2020). In addition, multiplex gene expression analysis revealed an up-regulation of genes involved in type I IFN signaling, whereas the ISGs were dramatically downregulated in critical SARS-CoV-2 patients. Accordingly, the ISG score (based on the expression of six genes defining a type I IFN signature) was significantly decreased in critical than in mild-to-moderate patients (see **Figure 8b**).

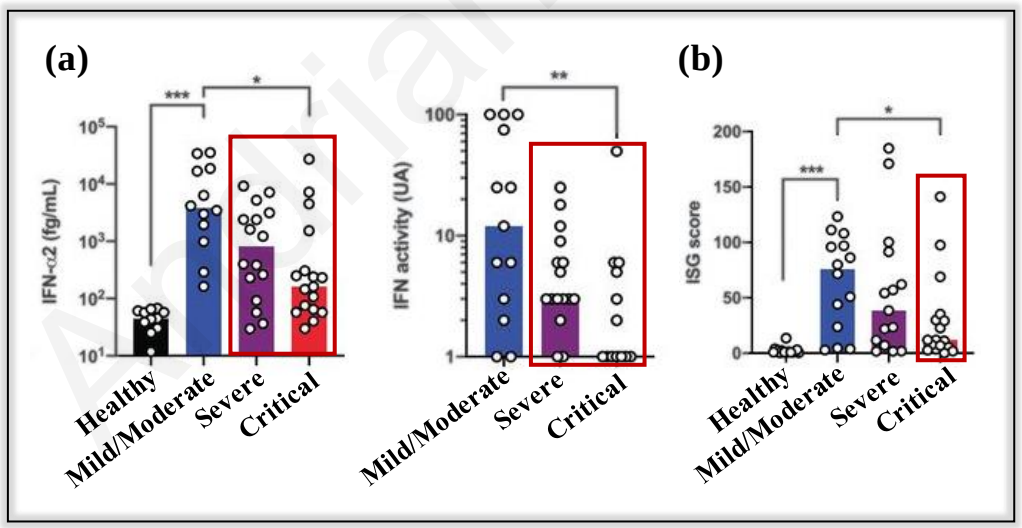

Figure 8. (a) *Impaired type I IFN production and activity in severe or critical COVID-19 patients.* ***(b)*** *Decreased ISG score in critical COVID-19 patients (Generated by Hadjadj et al., 2020).*

A host protein interactome study showed that SARS-CoV-2 ORF9b suppressed the expression of IFNβ in human HEK293T cells through interaction with the mitochondrial protein translocator of outer membrane 70 (TOM70), which is a critical regulator of MAVS-mediated antiviral signaling (see **Figure 9a**) (Jiang et al., 2020). Induction of TOM70 overexpression

was shown to largely rescue IFNβ expression from Orf9b-mediated inhibition (see **Figure 9b**). Moreover, ORF3b, a 22-amino acid short peptide encoded by SARS-CoV-2, was shown to suppress type I IFN induction by preventing the translocation of IRF3 into the nucleus (Konno et al., 2020). SARS-CoV-2 ORF6 and ORF8 were able to inhibit the expression of IFNβ and activation of ISGs in HEK293T cells transfected with different luciferase reporter plasmids (Li et al., 2020). Furthermore, SARS-CoV-2 membrane glycoprotein M was identified as an IFN antagonist, interacting with essential molecules of the cytosolic viral RNA sensing pathway, such as RIG-I, MDA5, and MAVS to blunt the formation of RLR-MAVS-TRAF3-TBK1 multiprotein complex (Zheng et al., 2020). Xia et al. showed that the NSP1 nonstructural protein of SARS-CoV-2 attenuated innate IFN response by blocking signal transducer and activator of transcription 1 (STAT1) phosphorylation (Xia et al., 2020).

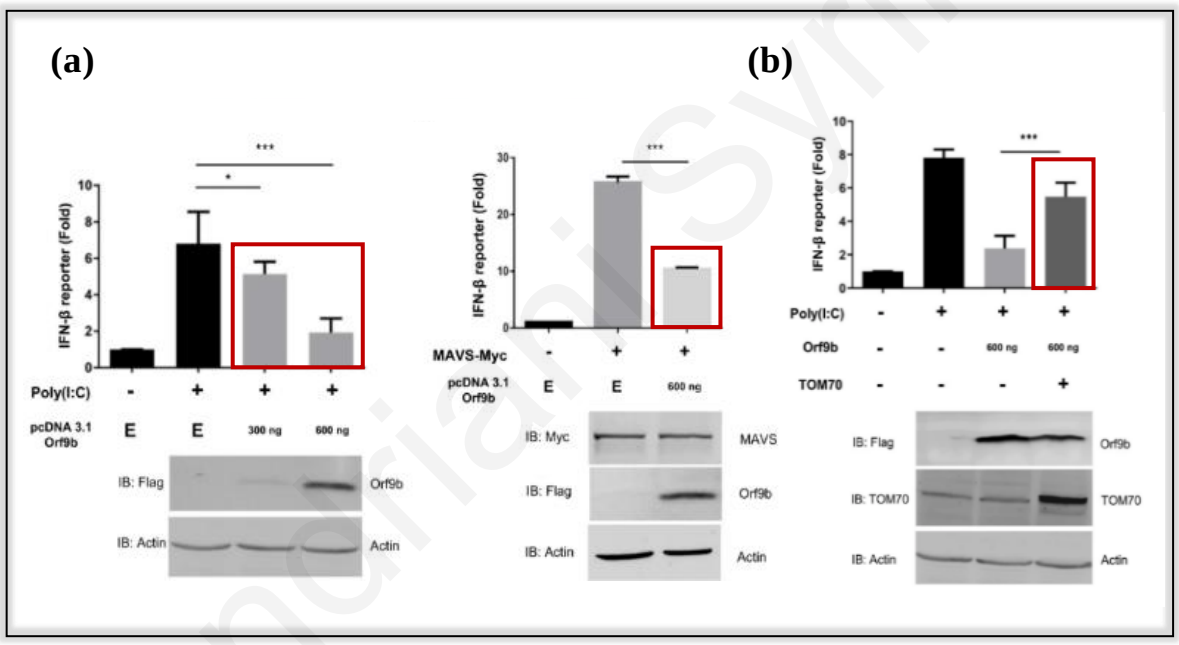

Figure 9. (a) *Suppressed IFNβ expression in HEK293T cells in the presence of SARS-CoV-2 ORF9b and TOM70.* ***(b)*** *TOM70 overexpression rescued IFNβ production in HEK293T cells in the presence of SARS-CoV-2 ORF9b (Generated by Jiang et al., 2020).*

Paradoxically, a single-cell RNA sequencing (scRNA-seq) analysis showed that several ISGs were upregulated in PBMCs from a COVID-19 patient with severe disease compared with patients who had mild infection (Zhu et al., 2020). In another scRNA-seq study of PBMCs from seven patients hospitalized for COVID-19, various ISGs were upregulated, especially in classical monocytes, but the ISG signature was not uniform within cell types and across patients (Wilk et al., 2020). Moreover, a transcriptomic sequencing analysis on bronchoalveolar lavage fluid (BALF) cells of eight COVID-19 patients revealed elevated expression of numerous ISGs in addition to a significant increase in the expression levels of proinflammatory cytokine and

chemokine genes, indicating a robust IFN response in SARS-CoV-2 infection (Zhou et al., 2020). Longitudinal immune profiling of patients with moderate or severe COVID-19 demonstrated that plasma levels of IFNα were sustained at higher levels in patients with severe disease, whereas IFNα levels declined in patients with moderate COVID-19 during the course of the infection (see **Figure 10**) (Lucas et al., 2020).

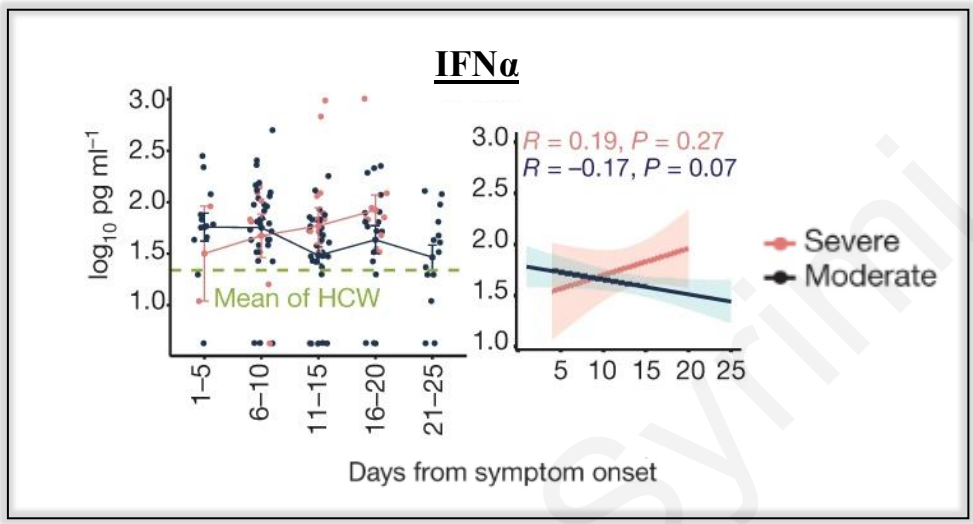

Figure 10. *Upregulation of IFNα in severe COVID-19 patients (Generated by Lucas et al., 2020).*

2.1.5 Dysfunctional immune responses and cytokine storm

SARS-CoV-2 infection and the destruction of lung tissue initiates a rapid and coordinated immune response, involving the activation and recruitment of immune cells at the site of infection, and the subsequent secretion of various cytokines and chemokines that prime adaptive T and B cell immune responses (Tay et al., 2020). In most individuals, this process leads to clearance of the virus, and minimal lung inflammation and lung damage, the immune response recedes, and patients recover. However, in some cases, aberrant immune responses caused by a dysregulated host immune system result in an excessive inflammatory cytokine release, eventually inducing a phenomenon known as "cytokine release syndrome" or "cytokine storm" which contributes to the occurrence of fatal complications and poor prognosis in SARS-CoV-2 infection (Mehta et al., 2020, Henderson et al., 2020). The term cytokine storm was first coined in 1993 in the context of graft-versus-host disease, and later, in various pathological conditions such as cancers, pathogen infections, autoimmune conditions, organ transplantation, immunotherapies, and, most recently, in COVID-19 (Wadia and Tambur, 2008, London et al., 2010, Grupp et al., 2013, Kumar, 2020). Cytokine storm is a fast-developing, life-threatening immune condition caused by a dysregulated overproduction of

circulating proinflammatory cytokines and immune-cell hyperactivation (Mangalmurti and Hunter, 2020). Several lines of evidence have revealed the components and characteristics of the cytokine storm in severe COVID-19 patients, which are composed of an array of pro-inflammatory effector cytokines, including IL-1β, IL-2, IL-6, IL-7, IL-10, TNF-α, IFN-γ, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as chemokines, such as macrophage inflammatory protein 1 alpha (MIP1α), MIP1β, and monocyte chemoattractant protein-1 (MCP-1) (Huang et al., 2020, Liu et al., 2020, Nile et al., 2020, Lucas et al., 2020, Ronit et al., 2021). Among these, IL-6, IL-10, and IL-1β were the three most increased cytokines in COVID-19 patients who developed severe disease (Diao et al., 2020, Dhar et al., 2021). This overwhelming inflammatory response can lead to ARD aggravation and widespread tissue damage resulting in multiorgan failure, and death if treatment is not adequate (Mangalmurti and Hunter, 2020). Therefore, a better understanding of the underlying pathways driving this robust cytokine release is extremely important for the development of precise diagnosis and effective therapeutic strategies.

2.1.6 The role of IL-6 signaling in COVID-19 cytokine storm

IL-6 is a pivotal cytokine with a diverse array of functions relevant to immunity, inflammation, hematopoiesis, tissue homeostasis and metabolism (Bordon, 2014, Hasegawa et al., 2016, Jones et al., 2018). Significantly increased serum levels of circulating IL-6 have been commonly observed in COVID-19-infected individuals with severe disease and were found to be associated with adverse clinical outcomes (Price et al., 2020, Ruan et al., 2020, Blanco-Melo et al., 2020, Moore and June, 2020). Excessive IL-6 production can impair the ability of these patients to mount a sufficient anti-inflammatory response, leading to the development of a cytokine storm.

IL-6 can act via two distinct signaling pathways referred to as classic cis-signaling or trans-signaling. In the classic IL-6 signaling pathway, IL-6 binds to the membrane-bound IL-6 receptor (IL-6R) forming an IL-6–IL-6R complex, which subsequently associates with a second protein, the transmembrane glycoprotein 130 (gp130), leading to dimerization of gp130 and activation of the intracellular signaling cascades Janus kinase (JAK)–signal transducer and activator of transcription (STAT) and MAPK (Scheller et al., 2014, Hunter and Jones, 2015). Interestingly, expression of IL-6R is restricted to a few cell types, such as hepatocytes, some epithelial cells, and some leukocytes, whereas the gp130 is ubiquitously expressed, possibly explaining the pleiotropic activities of IL-6 (Schaper and Rose-John, 2015). Activation of the

classic cis-signaling exerts pleiotropic effects on both innate and adaptive immune cells, which are manifested as increased differentiation of T-helper type 17 (Th17), CD8+ cytotoxic T, and B cells, and decreased development of regulatory T (Treg) cells, among other lymphocytic changes. In IL-6 trans-signaling pathway, high circulating concentrations of IL-6 bind to the soluble form of IL-6R (sIL-6R), with the agonistic complex of IL-6 and sIL-6R then binding to membrane-bound gp130, even on cells that lack IL-6R (Kang et al, 2019). The resultant IL-6–sIL-6R–JAK-STAT3 signaling is then activated only in cells with absent expression of IL-6R, such as endothelial cells and vascular smooth muscle cells (VSMCs). This results in a systemic "cytokine storm" involving the activation and secretion of different mediators like MCP-1, vascular endothelial growth factor (VEGF), IL-8, and additional IL-6, as well as the reduction of E-cadherin expression on endothelial cells (Tanaka et al., 2016). Increased secretion of VEGF and reduced expression of E-cadherin can lead to vascular permeability and leakage, which contribute to the pathophysiology of severe SARS-CoV-2 infection, including hypotension and pulmonary dysfunction in COVID-19-associated cytokine storm (Moore and June, 2020). Additionally, rapidly produced IL-6 promotes the release of various acute-phase proteins, including c-reactive protein (CRP), serum amyloid A, hepcidin, thrombopoietin (TPO), complement 3 (C3), fibrinogen, and ferritin in hepatocytes. An increase in the concentration of these serum proteins accompanies inflammation and severe infection.

2.1.7 SARS-CoV-2 triggered NLRP3-mediated pyroptosis and cytokine storm

Cytopathic viruses, including SARS-CoV-2, kill infected cells as part of the virus replicative cycle, causing high levels of virus-linked pyroptosis accompanied by secretion of inflammatory mediators and intracellular contents, which digest the extracellular matrix and produce a strong inflammatory response (Chen et al., 2019, Park et al., 2020). Pyroptosis is a highly inflammatory form of lytic-programmed cell death regulated by unique sets of critical inflammatory caspases that coordinate biological effects (Fink and Cookson, 2005). Although traditionally defined as CASP-1-mediated cell death, previous studies have revealed several other caspases capable of triggering pyroptosis, including the apoptotic effector CASP-3, murine CASP-11, and its human orthologs CASP-4 and CASP-5. In the CASP-1-dependent classical pyroptosis pathway, recognition of inflammatory ligands induces the formation of large, cytoplasmic multiprotein cytosolic complexes known as inflammasomes (Zheng et al., 2020). NLRP3, the most broadly activated inflammasome sensor is triggered in response to a wide array of exogenous stimuli and some endogenous host danger signals such as ion efflux,

reactive oxygen species (ROS), and metabolic dysregulation, leading to the activation of the proteolytic enzyme CASP-1. Upon activation, CASP-1 catalyzes proteolytic processing of proinflammatory cytokines IL-1β and IL-18 into their functional cytokine forms. Additionally, mature caspase-1 cleaves the pyroptotic executor protein gasdermin D (GSDMD) to its active form, which oligomerizes and forms nonselective pores in the plasma membrane, mediating the release of cellular contents, including the key inflammatory cytokines IL-1β and IL-18 and inducing pyroptosis (Huang et al., 2021). As a result of pyroptosis, or other forms of necrotic cell death, the enzyme lactate dehydrogenase (LDH) is released.

Increased levels of LDH were detected in the blood of patients with COVID-19, which strongly correlated with the development of severe disease (Huang et al., 2020, Wu et al., 2020). Additionally, IL-1β, an important cytokine released during pyroptosis, was elevated in COVID-19 cases with severe symptoms (Zhang et al., 2020). A study by Rodrigues et al. revealed that SARS-CoV-2 infection triggered NLRP3 inflammasome activation in primary human monocytes in vitro (see **Figure 11**) (Rodrigues et al., 2020).

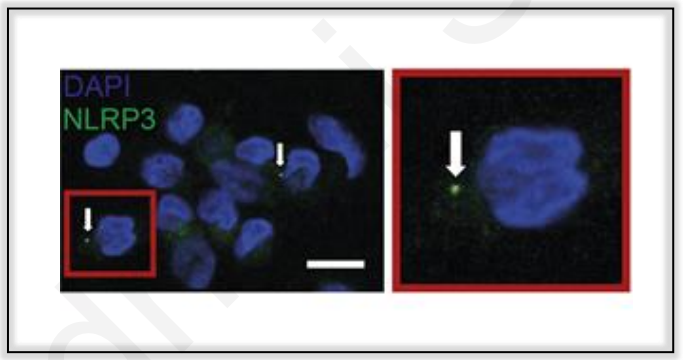

Figure 11. *A representative image of a human primary monocyte containing NLRP3 puncta (green, indicated by arrows) (Generated by Rodrigues et al., 2020).*

Ferreira et al. confirmed that SARS-COV-2 infection triggered NLRP3 inflammasome engagement in human primary monocytes with subsequent caspase-1 activation, IL-1ß maturation, GSDMD pore formation, and dysregulation of cytokine release, pointing toward a pyroptotic cell death (Ferreira et al., 2021). In addition, inhibition of SARS-CoV-2 replication, at protein translation levels, by atazanavir (ATV) prevented caspase-1-dependent lytic monocyte death. Consistently, lower levels of IL-1β, IL-6, TNF-α, and LDH were detected in SARS-CoV-2-infected monocytes treated with ATV. Importantly, targeting NLRP3 inflammasome by MCC950, a potent and selective NLRP3 inhibitor, suppressed SARS-CoV-

2 induced immune overactivation and thus alleviated COVID-19 immunopathology in lung tissues of hACE2 transgenic mice (Zeng et al., 2021).

In a recent paper, Junqueira et al. demonstrated antibody-mediated SARS-CoV-2 infection of blood monocytes via fragment crystallizable gamma receptors (FcγRs), which in turn triggered the activation of NLRP3 and absent in melanoma 2 (AIM2) inflammasomes (Junqueira et al., 2022). The investigators also observed that pyroptosis-specific biomarkers, including GSDMD, IL-1RA, IL-18, and LDH were elevated in the plasma of patients who developed severe disease compared with those with mild or moderate COVID-19. Blocking monocyte FcγRs, CD16 (FcγRIIIa) and CD64 (FcγRI) or depleting plasma immunoglobulin G (IgG), drastically inhibited viral uptake and replication, assessed by Neon Green (NG) fluorescence, whereas blocking the other receptors or depleting IgA had no significant effect on infection (see **Figure 12**).

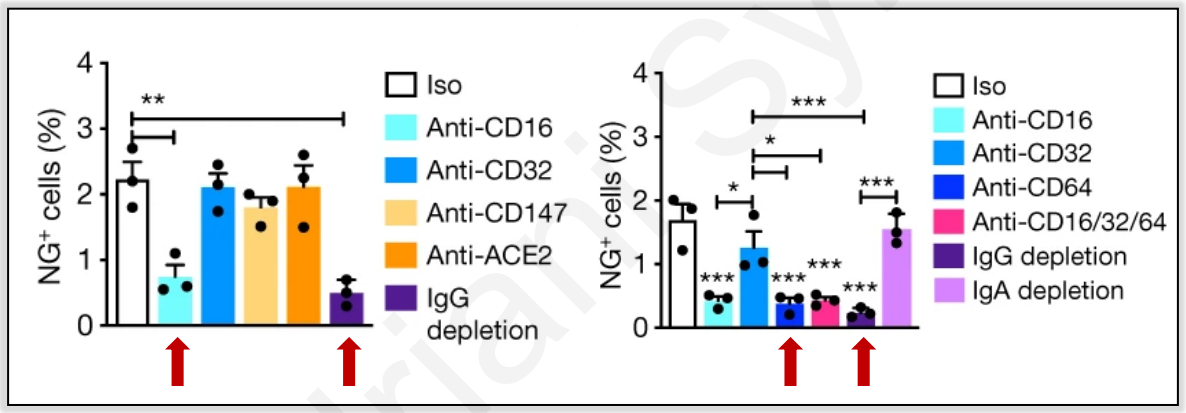

Figure 12. *Blockage of CD16 and CD64 monocyte receptors or IgG depletion strongly inhibited SARS-CoV-2 infection (Generated by Junqueira et al., 2022).*

These findings indicate that monocyte SARS-CoV-2 infection is independent of ACE2, the canonical viral entry receptor for SARS-CoV-2 but is mediated by CD16 and/or CD64 and requires opsonization of the virus by host antibodies. Inflammasome activation was also detected in lung-resident macrophages, but not in infected epithelial and endothelial cells from lung autopsies from patients with COVID-19. In another study, the same authors showed that pharmacological inhibition of caspase-1 and NLRP3 inflammasomes decreased the levels of proinflammatory cytokines and chemokines and reversed lung pathology in SARS-CoV-2-infected MISTRG6-hACE2 mice (Sefik et al., 2022). Taken together all these results suggest that inflammasome activation and pyroptosis are features of severe COVID-19 disease.

Previous studies have proved that SARS-CoV viroporin proteins E and ORF3a activate NLRP3 inflammasome by changing intracellular ionic concentrations and the production of ROS from

damaged mitochondria, suggesting a potentially similar effect of direct activation of the NLRP3 by SARS-CoV-2 proteins (Nieto-Torres et al., 2015, Chen et al., 2019). Xu et al. showed that ectopically expressed SARS-CoV-2 ORF3a primed and activated the NLRP3 inflammasome by triggering NF-κB-mediated expression of IL-1β, thus inducing cell death (Xu et al., 2022). Pan et al. identified a molecular mechanism by which SARS-CoV-2 promotes NLRP3 inflammasome activation to induce hyperinflammation. They showed that SARS-CoV-2 structural protein N specifically interacted with NLRP3 protein to facilitate the NLRP3 inflammasome assembly and activation, thereby leading to the expression of abundant inflammatory factors (such as IL-1β, IL-6, TNF-α, CCL2) and the development of mice lung injury (Pan et al., 2021). SARS-CoV-2 N-mediated inductions of IL-1β and IL-6 and lung injury in AAV-lung-N C57BL/6 mice were repressed by the administration of MCC950, a specific inhibitor of NLRP3 inflammasome activity, and a selective and irreversible inhibitor of caspase-1 Ac-YVAD-cmk, suggesting that NLRP3 inflammasome might be a potential immune intervention against severe COVID-19 disease.

2.1.8 Cytokine storm and organ damage

Upon SARS-CoV-2 infection, the virus infects the respiratory epithelial tissue and activates local innate immune cells and epithelial cells to release various proinflammatory cytokines and chemokines such as IL-6, MIP1α, MIP1β, MCP1, and IP-10, which in turn attract macrophages, monocytes, and T cells from the circulation into the infected site, promoting further inflammation (with the addition of IFNγ produced by T cells) and creating a positive feedback loop. In a healthy immune response, the initial inflammation attracts adaptive immune cells, CD8+ and CD4+ T cells, to the lungs where they can directly recognize and kill infected cells before the virus spreads and also activate B cells to generate neutralizing antibodies (NAbs) against virus-specific antigens. However, in a dysfunctional immune response, this pro-inflammatory feedback loop empowers SARS-CoV-2 invasion recruiting additional immune cells to the site of infection and causing overproduction of systemic circulating cytokines like IL-2, IL-10, IFN-γ, TNF-α, and GM-CSF, which induce the occurrence of myelopoiesis with immature and dysfunctional neutrophils and emergency granulopoiesis that can further aggravate respiratory epithelium damage. In addition, the production of sustained and excessive circulating cytokines, triggers macrophage activation (macrophage activation syndrome, MAS) and erythro-phagocytosis (hemophagocytic lymphohistiocytosis, HLH), resulting in anemia as well as gives rise to perturbation of vascular hemostasis, resulting in capillary leak syndrome and thrombosis (Engelmann and Massberg,

2012). These events together lead to severe complications with a fatal outcome that are manifested as ARDS, disseminated intravascular coagulation (DIC), and multiorgan failure.

2.2 Adaptive immune response to SARS-CoV-2

The adaptive immunity, also referred to as specific or acquired immunity, is composed of two principal arms, including the cellular immunity carried out by T (CD8+ cytotoxic T and CD4+ T) cells and the humoral immunity mediated by B cells that elicit a protective immune response against pathogens in an antigen-specific manner (Garcia, 2019). During viral infection, an effective adaptive immune response plays a crucial role in eliminating the virus and preventing the disease progression (Liu et al., 2017).

2.2.1 T cell responses

Circulating activated SARS-CoV-2-specific CD4+ T and CD8+ T cells were detected seven days after the resolution of clinical symptoms in the blood of a patient who experienced non-severe disease, indicating substantial anti-viral immunity in recovered patients (Thevarajan et al., 2020). Using human lymphocyte antigen (HLA) class I and II predicted peptide "megapools" covering the entire SARS-CoV-2 proteome, Grifoni et al. found that all convalescent COVID-19 patients who had uncomplicated disease, generated CD4+ T cell responses and 70% established CD8+ memory responses to SARS-CoV-2 (Grifoni et al., 2020). Spike-specific CD4+ T cell responses were robust (see **Figure 13**) and correlated well with the magnitude of the anti-spike RBD IgG and IgA titers.

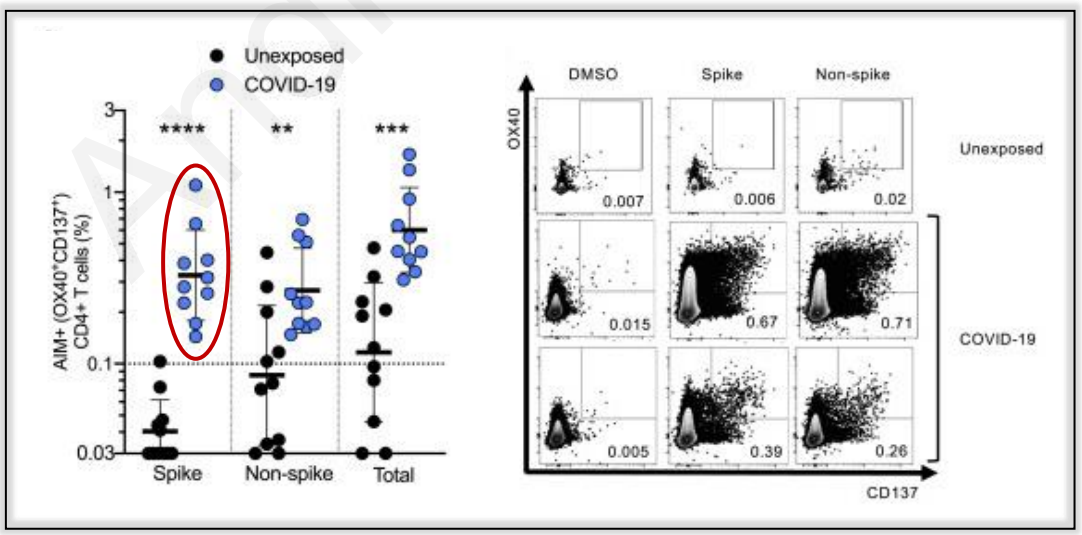

Figure 13. *SARS-CoV-2 spike-specific CD4+ T cell responses (OX40+CD137+) in 100% of COVID-19 cases (Generated by Grifoni et al., 2020).*

CD4+ T cell responses in COVID-19 cases were also directed against the SARS-CoV-2 M and N proteins, with additional responses specific for SARS-CoV-2 nsp3, nsp4, and ORF8. Regarding SARS-CoV-2 CD8+ T cell responses, spike protein and M were recognized, and significant reactivity was noted for other antigens with at least eight SARS-CoV-2 ORFs targeted. Importantly, SARS-CoV-2-reactive CD4+ T cells were also detected in ~40%–60% of unexposed healthy participants in their study, suggesting the possibility of pre-existing cross-reactive immunity (immune memory) between SARS-CoV-2 and seasonal "common cold" human coronaviruses (HCoVs), HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. Mateus et al. using peptide megapools in combination with human blood samples derived from pre-pandemic donors, provided direct evidence that these reactive CD4+ T cells in SARS-CoV-2-unexposed individuals were HCoV-specific memory T cells (Mateus et al., 2020). Another group of investigators provided evidence supporting the presence of memory and naïve cross-reactive CD8 T cells against SARS-CoV-2-derived peptides in non-exposed individuals (Quiros-Fernandez et al., 2021). Importantly, the work of Tan et al. revealed that early induction of functional SARS-CoV-2-specific T cells in patients with mild COVID-19 disease (specific for nucleoprotein, ORF7/8, ORF3a, membrane, and spike proteins), accelerated viral clearance (Tan et al., 2021).

2.2.2 Lymphopenia in COVID-19

Lymphopenia (also known as lymphocytopenia), a marker of impaired cellular immunity, with significantly reduced counts and percentages of peripheral lymphocytes was commonly observed in the blood of many individuals infected with SARS-CoV-2, especially in severe cases (Chen et al., 2020, Liu et al., 2020, Tan et al., 2020). More specifically, in a descriptive and predictive study of Tan et al., the blood lymphocyte percentage (LYM%) was found to be lower than 20% in patients with severe COVID-19 (Tan et al., 2020). Further analysis demonstrated, a significant reduction in the counts of total T cells, peripheral blood CD4+ and CD8+ T cells in SARS-CoV-2-infected patients, especially in patients requiring ICU (see **Figure 14**) (Diao et al., 2020). Additionally, Qin et al. found an increased percentage of naive helper T (Th) cells and a smaller percentage of memory helper T (Th) cells in severe cases compared with non-severe cases (Qin et al., 2020). Patients with severe COVID-19 also had decreased levels of Treg cells. Lymphocyte depletion is a common feature observed in several other infections, although it seems to be more rapid, long-lasting, and profound in COVID-19

disease (Fox et al., 2012, Russell et al., 2017). These data indicate that lymphopenia can be used as an effective and reliable indicator of COVID-19 disease severity and outcome.

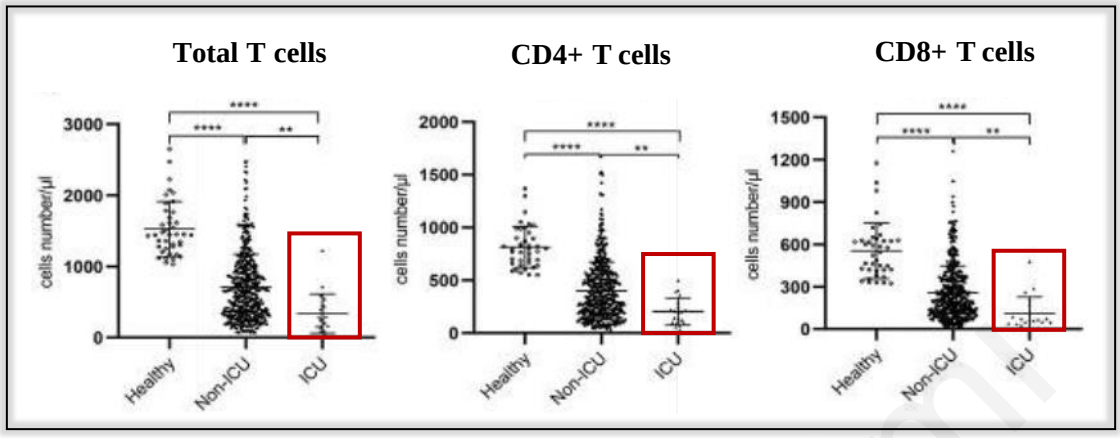

Figure 14. *Decreased T cell numbers in ICU patients (Generated by Diao et al., 2020).*

2.2.3 Potential mechanisms responsible for T cell depletion

Several mechanisms have been proposed to account for lymphocyte deficiency during SARS-CoV-2 infection. (1) Cytokine-mediated cell death might be responsible for the decrease in lymphocyte count. Diao et al. showed that the decreased numbers of total T cells were inversely correlated with serum concentrations of TNFα, IL-6, and IL-10 in COVID-19 patients, suggesting that increased production of inflammatory cytokines might drive the depletion of T cell populations that accompanies disease progression (see **Figure 15**) (Diao et al., 2020).

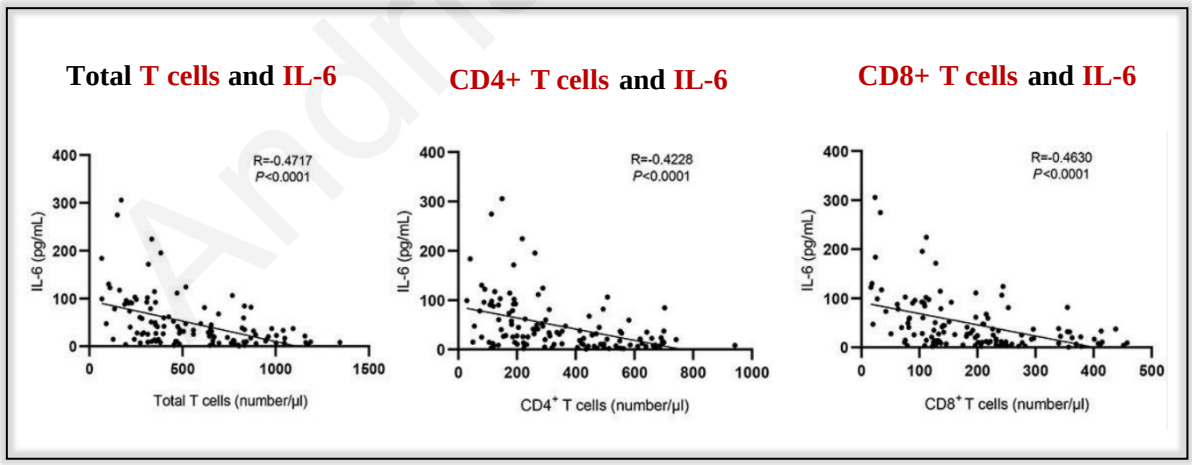

Figure 15. *Relationship between T cell numbers and IL-6 levels (Generated by Diao et al., 2020).*

(2) Moreover, the SARS-CoV-2 virus may directly induce severe tissue damage of secondary lymphoid organs spleen and lymph nodes, leading to further impairment of lymphocytes, which is supported by the observations of pathological alterations like spleen atrophy and lymph node necrosis, as well as reduced lymphocyte numbers (Li et al., 2020, Cao, 2020, Tan et al., 2020).

In a preprint study of Feng et al., in situ terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining revealed that SARS-CoV-2 infected spleen and lymph nodes manifested strong lymphocyte apoptosis, and this was associated with enhanced expression of the death receptor Fas in virus infected tissue, indicating that activation-induced cell death (AICD) may cause the reduction in T lymphocytes (Feng et al., 2020). (3) The occurrence of lymphopenia might also involve the inhibition of lymphocytes by metabolic molecules produced by metabolic disorders like hyperlactic acidemia. Increased blood lactic acid levels were detected in patients with severe COVID-19, which may suppress lymphocyte proliferation (Tan et al., 2020). (4) Finally, SARS-CoV-2 may directly infect T lymphocytes through binding of S protein to ACE2 receptor, the primary receptor for SARS-CoV-2 entry into the target cells, resulting in T cell death. However, some studies have demonstrated that T cells barely express surface ACE2, which raises the possibility of the presence of additional receptors that permit the entry of SARS-CoV-2 virus into these cells (Zhou et al., 2020). In a recent paper, Shen et al. showed that SARS-CoV-2 infected T cells, preferably activated CD4 + T cells, in an ACE2-independent manner and induced pronounced T cell death in vitro (Shen et al., 2022). The apoptosis of SARS-CoV-2-infected T lymphocytes was probably dependent on mitochondrial ROS–hypoxia pathways. The authors also showed that lymphocyte function-associated antigen-1 (LFA-1), the protein that is exclusively expressed on the surface of many leukocytes, was able to mediate SARS-CoV-2 infection in T cells.

2.2.4 Lymphocyte exhaustion in COVID-19

In addition to the abnormal reduction in cell number, the remaining lymphocytes in COVID-19 patients were functionally exhausted. Exhausted lymphocytes are a type of dysfunctional cells hallmarked by progressive loss of effector functions, increased and sustained expression of inhibitory receptors, metabolic defects, decreased production of effective cytokines and poor memory recall (McLane et al., 2019). T cells in patients with COVID-19 exhibited profound functional exhaustion characterized by increased expression of the T cell exhaustion markers, programmed cell death protein-1 (PD-1), and T cell immunoglobulin and mucin domain-3 (Tim-3) (Diao et al., 2020). Expression of PD-1 and Tim-3 on the surface of CD8+ T cells increased as patients progressed from prodromal to overtly symptomatic disease stages, and peak levels were observed in severe conditions (see **Figure 16**). Another investigation reported exhaustion phenotypes of cytotoxic lymphocytes, including NK and CD8+ T cells with an upregulated level of natural killer group 2 member A-positive (NKG2A) inhibitory receptor in the peripheral blood of COVID-19 patients (Zheng et al., 2020). The ability to produce

CD107a, IFN-γ, IL-2, granzyme B, and TNF-α was diminished in exhausted NK and CD8+ T cells. Importantly, the total number of CD8+ T and NK cells was restored with decreased expression of NKG2A in patients convalescing after antiviral therapy. These alterations strongly suggest that SARS-CoV-2-induced NKG2A expression may be associated with functional exhaustion of cytotoxic lymphocytes and disease progression in the early stage of COVID-19. Since an elevated expression of PD-1, Tim-3 and NKG2A was responsible for lymphocyte exhaustion, downregulation or inhibition of these molecular biomarkers may hopefully reverse the functional exhaustion of antiviral lymphocytes during SARS-CoV-2 infection.

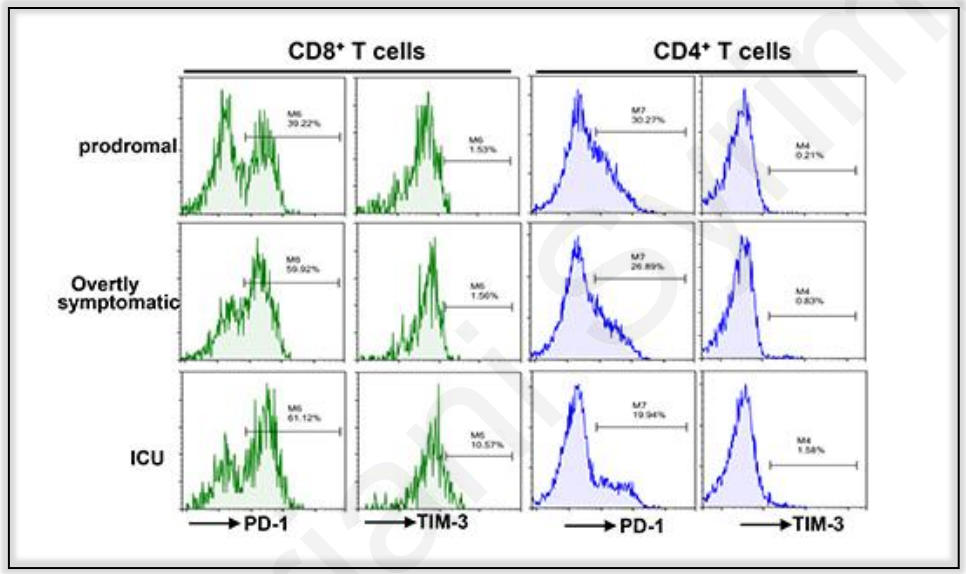

Figure 16. *Dynamic profile of PD-1 and TIM-3 exhaustion markers expression on T cells in 3 COVID-19 patients (Generated by Diao et al., 2020).*

2.2.5 B cell responses

SARS-CoV-2 infection stimulates rapid production of neutralizing antibodies (NAbs) that can recognize different viral antigens, preventing the virus from entering human host cells that express its entry receptor ACE2. In SARS-CoV-2, the primary target of neutralizing antibodies is the highly immunogenic spike protein with its S1, S2, and RBD domains, which enables viral access to the host cell, as well as the abundantly expressed and highly conserved nucleocapsid protein. Elevated immunoglobulin M (IgM) and IgG SARS-CoV-2-binding antibodies were observed in the blood of non-severe COVID-19 patients before symptomatic recovery, which persisted for at least 7 days following full resolution of symptoms (Thevarajan et al., 2020). Importantly, cross-section and longitudinal studies showed that serum levels of NAbs against SARS-CoV-2 peaked within the first few weeks after infection and declined

subsequently, indicating that immunity to the virus cannot be long-lived after recovery (Seow et al., 2020, Wajnberg et al., 2020, Isho et al., 2020, Muecksch et al., 2021). In a study of 285 patients with COVID-19 by Long et al., acute antibody responses to SARS-CoV-2 infection were reported. Within 17-19 days after symptom onset, 100% of patients tested positive for virus-specific IgG, and approximately 94.1% for virus-specific IgM 20–22 days post-symptom onset (See **Figure 17**) (Long et al., 2020). IgM antibodies appeared to decline after 3 weeks of clinical symptoms onset.

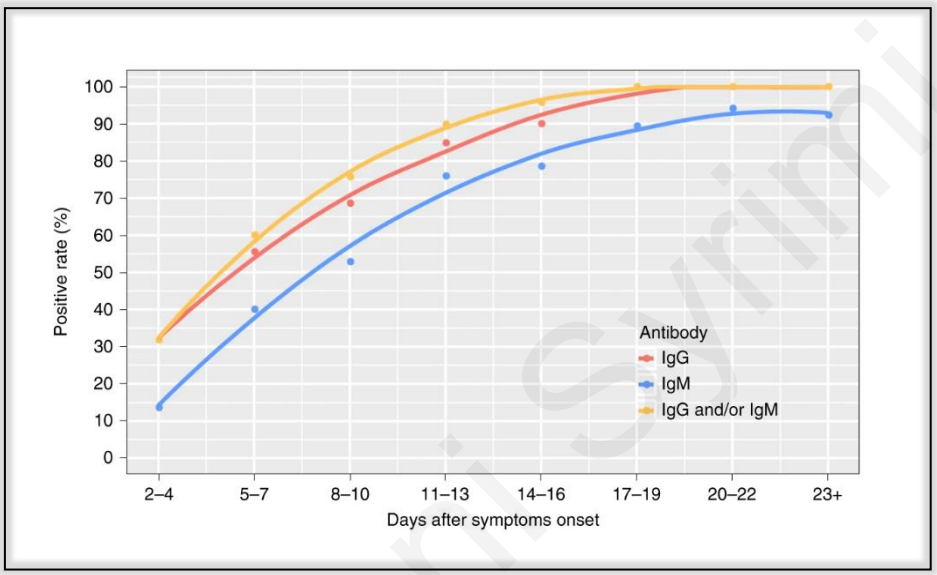

Figure 17. *Graph showing the positive rates of SARS-CoV-2 specific IgG and IgM antibodies over days after symptoms onset (Generated by Long et al., 2020).*

An interesting observation was that the group of patients with severe symptoms produced higher levels of IgM and IgG antibodies compared to those in the non-severe group. Furthermore, different types of seroconversions were reported, including synchronous seroconversion of IgG and IgM, IgM seroconversion earlier than that of IgG, and IgM seroconversion later than that of IgG. IgM antibodies appeared to decline after 3 weeks of clinical symptoms onset. Subsequently, Lou et al. also described the characteristics of the SARS-CoV-2-specific antibody response. Specifically, they found that the seroconversion rate for both IgM and IgG in COVID-19 patients was 93.8%. The median seroconversion times for IgM and IgG were 10 and 12 days after symptom onset, respectively.

2.2.6 Antibody-dependent enhancement (ADE)

B cells are considered protective in SARS-CoV-2 infection by producing NAbs to inhibit viral entry into host cells (neutralization) (Nielsen et al., 2020). However, in some cases these B cell-produced NAbs instead of offering protection, paradoxically amplify viral infection or trigger harmful immunopathology through the phenomenon of antibody dependent enhancement (ADE) (Lee et al., 2020). ADE can occur when preexisting non-neutralizing antibodies or antibodies at sub-neutralizing levels recognize and bind to the viral surface antigens, and then use their Fc portion to interact with the FcγRs that are expressed by immune cells such as monocytes, macrophages, and dendritic cells, leading to enhanced viral infection and replication (see **Figure 18a**). Additionally, ADE triggers increased immunopathology and inflammation by immune complex formation or by excessive antibody Fc-mediated effector functions (see **Figure 18b**). The ADE phenomenon has been observed in a number of viral infections, including dengue, human immunodeficiency virus (HIV), Ebola, Flavivirus, SARS-CoV, and MERS-CoV (Peiris and Porterfield, 1979, Willey et al., 2011, Katzelnick et al., 2017, Kuzmina et al., 2018, Wan et al., 2020).

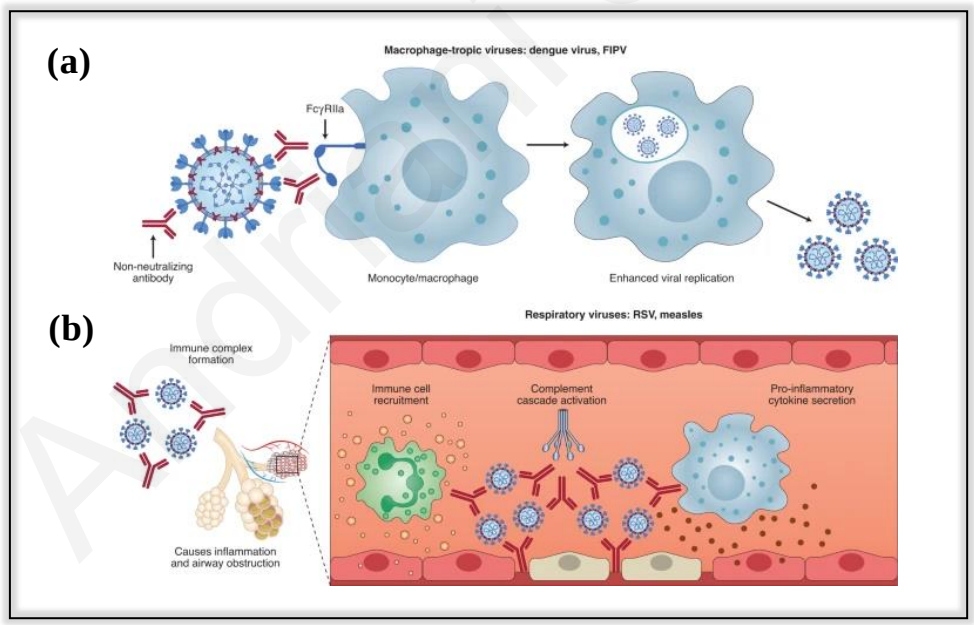

Figure 18. Two main ADE mechanisms in viral disease. (a) *Enhanced antibody-mediated virus uptake into Fc gamma receptor IIa (FcγRIIa)-expressing macrophages and monocytes, leading to increased viral infection and replication.* ***(b)*** *Fc-mediated antibody effector functions can enhance respiratory disease by initiating a powerful immune cascade that causes inflammation and airway obstruction (Generated by Lee et al., 2020).*

Some studies have revealed a positive correlation between increased COVID-19 severity and strong antibody responses, implying the potential involvement of ADE in SARS-CoV-2 infection (Zhao et al., 2020, Long et al., 2020). Wang et al. reported that the monoclonal antibody (mAb) MW05 targeting the RBD domain of SARS-CoV-2 S protein may also induce ADE activity to Fc gamma receptor IIB (FcγRIIB)-expressing cells in vitro, providing the first evidence that SARS-CoV-2 mAbs had an ADE effect in vitro (Wang et al., 2020). The ADE activity of MW05 was completely abolished after the administration of an engineered antibody with LALA mutation (L234A and L235A) to the Fc region (MW05/LALA antibody). Further, potent prophylactic and therapeutic efficacy of MW05/LALA antibody was observed in a rhesus monkey SARS-CoV-2 infection model. In a more recent paper, the same authors identified a novel mechanism of ADE of SARS-CoV-2 pseudoviral infection in vitro (Wang et al., 2022). More specifically they found that the two neutralizing mAbs, MW05 and MW01, exhibited significant ADE effects on FcγRIIB-expressing human primary B cells. The bivalent interaction of these two mAbs with the SARS-CoV-2 S trimer was required for the ADE of SARS-CoV-2 pseudoviral infection. To facilitate the development of new vaccines or antibody-based therapies for COVID-19, additional research about ADE in SARS-CoV-2 infection is required.

3. DISCUSSION

The COVID-19 outbreak, caused by SARS-CoV-2, has lasted for more than two years now and continues to pose a major threat to global public health. A range of measures have been implemented to prevent the spread of COVID-19, including the wearing of masks, washing and disinfecting hands, social distancing, active testing, and restrictions on social gatherings. Although these measures can effectively reduce the transmission of SARS-CoV-2, do not provide a fundamental solution. Vaccination against COVID-19 has been shown to be an effective long-term way to prevent infection or to suppress its detrimental or even fatal manifestations (Creech et al., 2021). Another interesting way of decreasing susceptibility or the risk of developing severe disease may be pre-activation of the host antiviral innate immunity to a state reminiscent of the upper airways of children, a concept referred to as 'trained immunity', which is functionally similar to building immunological memory (Netea et al., 2020, Loske et al., 2022). Trained immunity describes the concept that — upon a primary challenge, such as vaccination or infection, the innate immune cells undergo epigenetic and metabolic reprogramming that results in enhanced immune responses against subsequent triggers as well as in improved host defense and survival. The Bacillus Calmette–Guérin (BCG) vaccine, a live attenuated vaccine designed to provide protection against tuberculosis, has been reported to reduce the incidence of respiratory tract infections, a protective effect proposed to be mediated by trained immunity (Giamarellos-Bourboulis et al., 2020, O'Neill and Netea, 2020). In the context of COVID-19, previous studies have suggested that countries who adopt a national BCG vaccination policy may have a lower number of infections and reduced mortality from COVID-19 (Gursel and Gursel, 2020, Escobar et al., 2020). Moreover, in a large cohort study of healthcare workers (HCWs) the authors observed protective and nonspecific association between a history of BCG vaccination and decreased rates of SARS-CoV-2 infection (Noval Rivas et al., 2020).

The human immune responses, including both innate and adaptive immunity, against SARS-CoV-2 are essential for controlling and resolving the viral infection. Innate immunity, along with physical and chemical barriers, constitutes the first line of host defense against SARS-CoV-2. Activation of the innate immune system is initiated by the recognition of incoming single-stranded RNA or other RNA compositions, and replicative intermediates of the virus through an array of host innate antiviral sensors such as TLRs (e.g., TLR2 and TLR4) and RLRs (e.g., RIG-I, MDA5, LGP2). It has been shown that ligand binding to the RIG-I C-terminal domain activates the ATPase activity to induce conformational changes in RIG-I,

which enables RIG-I to interact with the adapter protein MAVS (Goubau et al., 2013, Takaoka and Yamada, 2019). This culminates in the kinase-dependent activation of both IRF-3 and NF-κB transcription factors, which participate in the induction of antiviral genes, including genes encoding type I and III IFNs to endow antiviral activities in host cells. Yamada et al. found that the helicase domain of RIG-I, but not the RIG-I C-terminal domain, selectively interacts with the 3′ untranslated region (UTR) of the SARS-CoV-2 RNA genome, resulting in impaired activation of the ATPase activity (Yamada et al., 2021). This unconventional RIG-I engagement misfires the activation of the downstream MAVS signaling pathway, which is in accordance with lack of type I and III IFN and proinflammatory cytokine inductions. This might explain the contradictory results with RIG-I described in this paper.

Downstream of innate immune sensing, the IFN signaling along with the formation of inflammatory cytokines are key features of the innate immune response, performing antiviral functions to promote viral clearance and stimulate adaptive immunity. Kim et al. proposed a mechanistic model that might explain the conflicting results regarding the type I IFN responses reported in patients with severe COVID-19 (Kim and Shin, 2021). After respiratory epithelial cells are infected, the newly synthesized proteins of SARS-CoV-2 block viral-recognition signaling and the production of type I and III IFNs, which results in an increased viral load due to the extensive uncontrolled replication of the virus in the host cells. The uninfected macrophages, monocytes, and DCs are stimulated by viral components through the host innate immune sensors TLRs, triggering the generation of large amounts of type I and III IFNs. The delayed but exaggerated IFN production from these cells further induces the accumulation and activation of monocytes and macrophages, thus leading to the production of excessive amounts of pro-inflammatory cytokines, such as TNF, IL-6, and IL-1β. Using IFNα receptor–deficient ($IFNAR^{-/-}$) and $IRF3/7^{-/-}$ C57BL/6J mice infected with SARS-CoV-2, Israelow et al. showed that type I IFN signaling was required for the recruitment of proinflammatory immune cells into the lungs of mice, but not for viral clearance (Israelow et al., 2020). Importantly, type I IFN responses might vary among individuals due to the presence of autoantibodies that block the action of certain IFNs or genetic variants that impair IFN signaling, conferring a high risk for severe COVID-19 (Zhang et al., 2020, Bastard et al., 2020).

Type I IFNs exhibit broad-spectrum antiviral activities, and therefore recombinant IFN-α and IFN-β are being investigated as a treatment option for patients with COVID-19. Lokugamage et al. found that SARS-CoV-2 was sensitive to the antiviral effects of recombinant type I IFN (recombinant IFN-α) in Vero E6 cells with a significant reduction in viral titers (Lokugamage

et al., 2020). The results of a randomized, double-blind, placebo-controlled, phase 2 pilot trial suggested that inhaled nebulized IFN-β-1a (SNG001) may be safe and efficacious in the treatment of mild and moderate COVID-19 (Monk et al., 2021). Additionally, in a retrospective study including 77 confirmed COVID-19 cases, treatment with nebulized IFN-α2b alone or in combination with arbidol (ARB), a broad-spectrum antiviral drug, significantly decreased the duration of detectable virus and inflammatory markers such as IL-6 and CRP (Zhou et al., 2020). However, given that exaggerated IFN responses contribute to hyper-inflammation and disease progression, the use of IFNs for the treatment of patients with COVID-19 may need to be restricted in the early stages of infection. Unfortunately, SARS-CoV-2 has evolved multiple evasion mechanisms to counteract human host defense programs resulting in enhanced replication and successful viral transmission (Li et al., 2020, Burke et al., 2021). Thus, understanding the underlying mechanisms by which SARS-CoV-2 escapes the host immune system and the IFN pathways that can counteract them is critical for developing specific treatments for COVID-19 disease.

The majority of people infected with SARS-CoV-2 exhibit a mild-to-moderate respiratory disease, and the infection is likely limited to the upper conducting airways. However, in severe cases, COVID-19 can develop into a life-threatening hyperinflammatory disease —cytokine storm—, caused by a dysregulated host response to infection and characterized by hyperproduction of different proinflammatory cytokines and excessive activation of immune cells. The cytokine storm can lead to severe clinical manifestations such as ARDS, multiple organ failure, and death in the most severe cases. The COVID-19 cytokine storm involves a higher number of inflammatory cytokines compared to the cytokine storm recognized in other conditions, thereby providing an explanation for the aggressive inflammatory responses observed in this disease. Lymphopenia, a hallmark of severe COVID-19, although relatively less common in other cytokine storm disorders, was frequently reported in COVID-19 cases, suggesting that the cytokine storm triggered by SARS-CoV-2 infection may be mainly attributed to innate—rather than adaptive immune cells (Fajgenbaum and June, 2020). Finally, compared with bacterial infection-induced cytokine storm such as sepsis, the treatment of COVID-19-associated cytokine storm is more challenging, because blocking cytokine signaling without effective anti-viral drug support may lead to worse outcomes, exacerbating the infection or even increasing the risk of secondary infections. Host immunomodulatory agents that inhibit the excessive cytokine production and hyper-inflammation, have been extensively evaluated for the treatment of severe COVID-19, and many others are under

investigation. The finding of elevated levels of IL-6, a leading inducer of COVID-19 cytokine storm, in patients with severe COVID-19 suggests that blocking IL-6 may be a potential therapeutic strategy for severe disease (Lucas et al., 2020). Tocilizumab, a recombinant humanized anti-IL-6 receptor-blocking monoclonal antibody was shown to improve the survival in hospitalized COVID-19 patients (Group, 2021). In a retrospective study of 21 COVID-19 patients with severe or critical illness, Xu et al. showed that tocilizumab rapidly improved the clinical outcomes in most patients within five days of administration, manifested as decreased serum C-reactive protein (CRP) levels, oxygen intake, and hospital stays, as well as the rapid recovery of the percentage of lymphocytes in peripheral blood (Xu et al., 2020). Another multicenter cohort study of 3924 critically ill patients with COVID-19 in ICUs across 68 hospitals in the United States showed that the risk of mortality was lower in patients treated with tocilizumab in the first 2 days of ICU admission compared with those patients who did not receive early tocilizumab intervention (Gupta et al., 2021). Giamarellos-Bourboulis et al. found that the IL-6 blocker tocilizumab partially restored decreased expression of human leukocyte antigen D related (HLA-DR) on CD14 monocytes in vitro, indicating that IL-6 may drive the downregulation of HLA-DR on monocytes (Giamarellos-Bourboulis et al., 2020).

Based on the current literature, this work has presented the host innate and adaptive immune responses against SARS-CoV-2 infection with a particular focus on the contribution of dysregulated host immune system to the development of a cytokine storm. Controlling the inflammatory responses and immune dysregulation may be as important as targeting the virus and its replication mechanisms. Importantly, the marked dysregulation of the immune system seen in severe cases of COVID-19 should serve as a warning in the development and evaluation of vaccines. We hope that with the continuously emerging new technologies, the development of more powerful vaccines for protection against serious illness as well as new therapeutic approaches, the COVID-19 pandemic will be under control in the near future.

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