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## Review

## SARS-CoV-2 mediated dysregulation in cell signaling events drives the severity of COVID-19

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## A B S T R A C T

A balance in immune response against an unfamiliar pathogen is crucial to eliminate the infection. A cascade of cell signaling events is immediately activated upon sensing the presence of SARS-CoV-2 by cellular toll like receptors in a natural host response manner against the invading virus. The ultimate aim of such innate immune signaling pathways is to provide a required level of protection to our bodies by interfering with the invader. However, if there is any loss in such balance, an impairment in immune system emerge that fails to control the regulated transcription and translation of signaling components. Consequently, excessive level of proinflammatory mediators release into the circulatory systems that ultimately cause “cytokine storm” and COVID-19 pathological syndromes. The limited production of interferons (IFNs), while excessive yield of pro-inflammatory cytokines followed by SARS-CoV-2 infection suggests an abnormal cell signaling event and explains the reasons of increased immunopathology and severity in COVID-19.

## Abbreviations

AKI	acute kidney injury
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
ASC	apoptosis associated speck-like protein containing a CARD
BMDM	bone marrow derived macrophage
CARD	caspase activation and recruitment domain
cfDNA	circulating free DNA
CRP	C-reactive protein
DAMP	danger associated molecular pattern
GSDMD	gasdermin D
IL-18BP	interleukin 18 binding protein
IL-1Ra	interleukin 1 receptor agonist
IFN	interferon
IRF	interferon regulatory transcription factor
LDH	lactate dehydrogenase
LPS	lipopolysaccharide
TLR	toll like receptor
MAPK	mitogen-activated protein kinase
mtDNA	mitochondrial DNA
mtROS	mitochondrial reactive oxygen species
MYD88	myeloid differentiation primary response 88
NET	neutrophil extracellular trap

NF-κB	nuclear factor kappa B
NLR	NOD like receptor
PRR	pattern recognition receptor
PAMP	pathogen associated molecular pattern
TRIF	TIR-domain-containing adapter-inducing interferon-β

## 1. Background

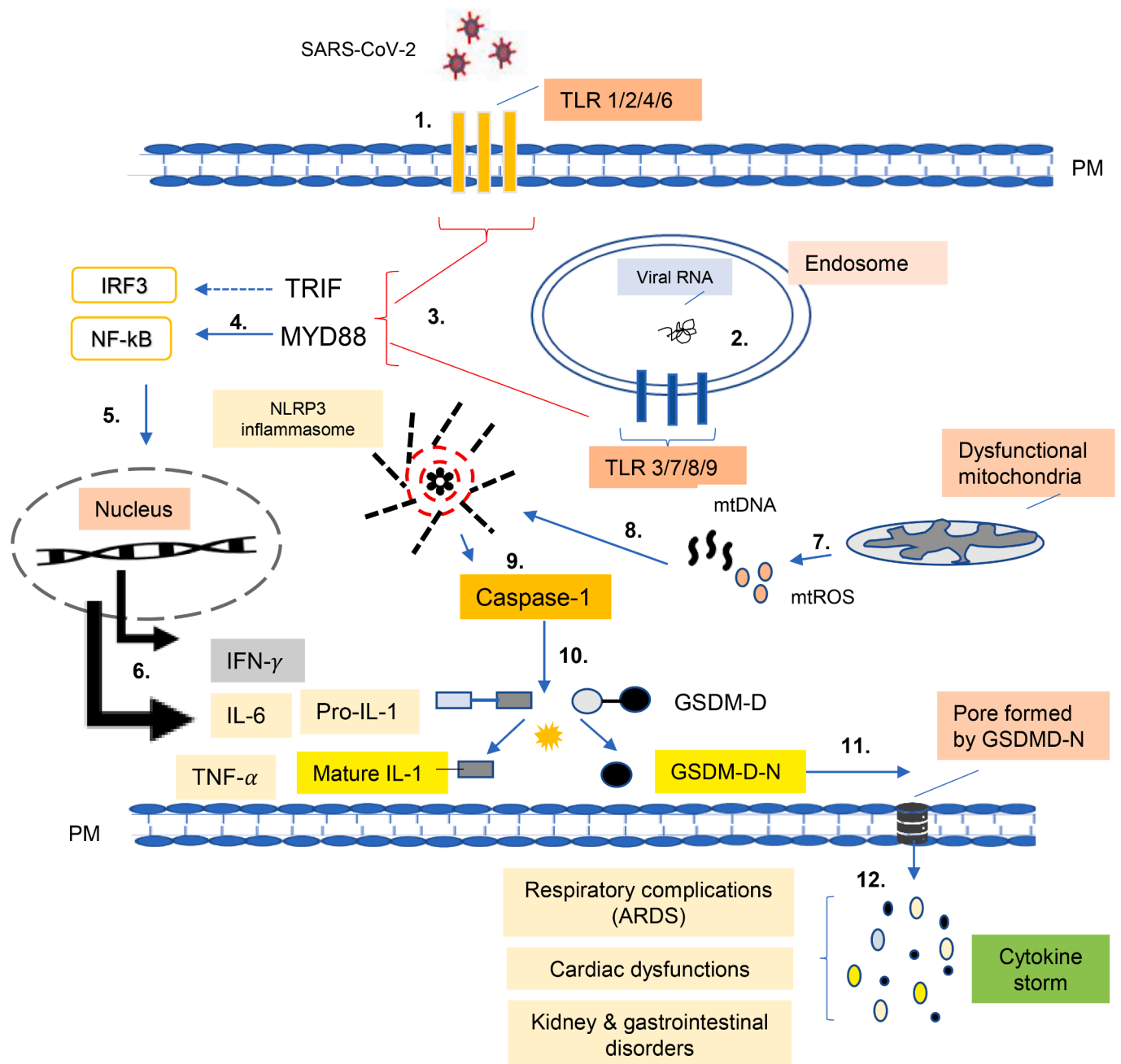
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible, rapidly mutating virus in beta-coronavirus sub-family that causes COVID-19 pandemic, a major concern at present. The symptoms of this diseases range from mild to severe respiratory illness. A common outcome of COVID-19 is “Cytokine storm” characterized by excessive activation of immune cells and the generation of pro-inflammatory cytokines (Su et al., 2021). The phenomenon of cytokine storm has been observed to induce apoptosis of epithelial and endothelial cells, vascular leakage and, finally, result in acute respiratory disease syndrome (ARDS), accompanied by other severe syndromes, and even death in most severe cases (Tian et al., 2020; Zhao et al., 2021a). By reviewing the reports and clinical findings of COVID-19, it has been suggested that Toll-like receptors (TLRs) pathways could be responsible for accelerating the pathogenesis of SARS-CoV-2 by promoting the activation of NF-κB pathway, inducing the formation of inflammasome, accelerating the release of

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inflammatory molecules and triggering pyroptosis (de Rivero Vaccari et al., 2020; Jung and Lee, 2021; Khanmohammadi and Rezaei, 2021; Manik and Singh, 2021; Zhao et al., 2021a). The combination of these dysregulated events at various stages of different innate immune responsive pathways are the main reasons for such imbalance. In addition to pathogen invasion and Pathogen-associated molecular patterns (PAMPs), the presence of several danger molecules existing into the cellular environments such as  $K^+$  efflux, oxidative stress, abnormal

presence of mitochondrial reactive oxygen species (mtROS) or mitochondrial DNA (mtDNA), impaired adipocyte function, telomere shortening can act as potential priming factors for abnormal activation of innate immune signaling (López-Reyes et al., 2020; Lara et al., 2020). As the presence of these risk factors are more prominent in certain group of peoples (especially immunocompromised and advanced aging), it is logical to implement why the severity and clinical outcome is more pronounced in those group of patients (Amin et al., 2022; López-Reyes



**Fig. 1.** Key events associated with cell signaling dysregulation and resulted pathological syndrome in COVID-19: (1) cell surface TLRs recognize SARS-CoV-2 antigenic epitopes, meanwhile, (2) endosomal TLRs recognize the virus nucleic acids, (3) the ligand induced conformational changes in the TLRs activate either adapter protein TRIF or MYD88. (4) The activated TRIF can induce IRF-3, while, MYD88 can induce NF- $\kappa$ B transcription factors. (5) The activated transcription factors then translocate inside nucleus to bind with DNA, and (6) initiate the transcription of multiple pro-inflammatory cytokines, chemokines and IFN. (7) On the other hand, in addition with viral PAMPs, the presence of ROS, cfDNA or different DAMPs released by dysfunctional organelles especially mitochondria, induce the formation of NLRP3 inflammasome (8, 9) The formation of NLRP3 inflammasome, further induce the activation of pro-caspase-1 into active caspase-1. (10) The catalytically active caspase-1 then initiates the catalysis of multiple pro-inflammatory cytokines (especially IL-1) and GSDMD into bioactive form. (11) The caspase-1 catalyzed GSDMD-N is then able to induce pore formation in the plasma membrane, (12) thus, the release of cytoplasmic contents including cytokines, chemokines and other harmful immune mediators into the extracellular space occur that give rise to cytokine storm and other COVID-19 pathological syndrome. PM, plasma membrane.

et al., 2020; Lara et al., 2020). In this review we will discuss current understanding of TLRs regulated cell signaling pathways in response to SARS-CoV-2 infection, the pattern of dysregulation in those pathways responding to either SARS-CoV-2 encoded protein or nucleic acids, the types of clinical outcomes arise due to the dysregulation, the major underlying cellular components involved with the triggering of severity and imbalance, and potential bio-signatures to confirm dysregulated cell signaling.

## 2. TLRs as PRR

Toll like receptors (TLRs) are germline encoded pattern recognition receptors (PRRs) that play a pivotal role in the activation of innate immunity through the recognition of special components of pathogens categorized as pathogen associated molecular patterns (PAMPs) (Akira et al., 2001). Among the 10 reported TLRs, TLRs 1, 2, 4, 5, 6, and 10 are located at the plasma membrane and recognize microbial membrane components, on the other hand, TLRs 3, 7, 8, and 9 are predominantly located within the endosomes and recognize microbial nucleic acids (Jung and Lee, 2021; Kawasaki and Kawai, 2014). The specific ligand induced conformational change of a particular TLR and subsequent alteration of adapter proteins determine the type of downstream signaling pathways to be activated. The major pathways involved with TLR transduction mainly include myeloid differentiation primary response 88 (MYD88) and TIR-domain-containing adapter-inducing interferon- $\beta$  (TRIF) dependent signaling cascades that can generate both pro-inflammatory cytokines and a type I/III IFN response, respectively (Mabrey et al., 2021). TLR 2/4/6 as well as TLR 7/8 and 9- induced MYD88 lead to the activation of NF- $\kappa$ B pathway through Tumor necrosis factor receptor (TNFR)- associated factor 6 (TRAF6) signaling, meanwhile, TLR 7/8/9 can indirectly activate IRF7 pathway through IRK4 dependent TRAF3 activation. Besides, TLR3 and TLR4- induced TRIF leads to the activation of IRF3 pathway through TRAF3 signaling (Khanmohammadi and Rezaei, 2021). The activated NF- $\kappa$ B and IRF3 pathway are involved with the production of pro-inflammatory cytokines and IFN. The pro-inflammatory cytokines can further trigger the formation of inflammasome with the help of caspase 1 (de Rivero Vaccari et al., 2020). The resulted cytokines and inflammatory mediators contribute to the elimination of viruses, although it can also harm the host due to persistent inflammation and tissue destruction. This leads to a competition between ongoing damage either from direct viral infection or the innate hyperinflammatory reactions responding to the protective innate and adaptive antiviral responses (Mabrey et al., 2021). As a result, the dysregulated immune system fails to provide enough protection (Fig. 1).

### 2.1. TLR regulated cell signaling pathways activated by SARS-CoV-2 infection

Like other viruses, the PAMPs of SARS-CoV-2 can also be recognized by TLRs (Jung and Lee, 2021; Mabrey et al., 2021). It has been suggested that either cell surface TLRs (TLR 1, 4, 6)- capable to recognize the viral proteins, or endosomal TLRs (TLR 3, 7, 8, 9)- capable to sense the ssRNA nucleic acid of SARS-CoV-2 can be involved with TLR signaling (Jung and Lee, 2021). Several evidences showed that the expression of MYD88, TLR1, TLR2, TLR4, TLR5, TLR8, and TLR9 was increased in patients with severe to critical illness (Khan et al., 2021; Zheng et al., 2021). Recently, a study showed that envelope protein (E) of SARS-CoV-2 can activate TLR2 dependent signaling pathways, as inhibition of TLR2 has protected mice from lethal SARS-CoV-2 infection (Zheng et al., 2021). Meanwhile TLR2 mediated recognition of spike protein has been observed by another study, in which the group showed that intraperitoneal injection of recombinant S protein triggered TLR2-dependent proinflammatory cytokine production in mice (Khan et al., 2021). Besides, ongoing studies also confirmed that the S protein leads to proinflammatory cytokine production in monocytes and

macrophages in a TLR4-dependent manner (Shirato and Kizaki, 2021; Zhao et al., 2021b; Zheng et al., 2021).

Endosomal TLRs (TLR3, 7, 8, and 9) are bound to sense the presence of pathogenic nucleic acid in the endosomal surface. Similar to other coronaviruses, SARS-CoV2 also carries a ssRNA that can be sensed by endosomal TLRs immediately after infection. A report confirmed that SARS-CoV-2 infected multicellular spheroids can induce the expression of TLR3 and 7 which can further stimulate the downstream pathways especially, IRF3 and NF- $\kappa$ B as well as lead to the production of pro-inflammatory cytokines and type 1 IFN (Bortolotti et al., 2021). Meanwhile, a number of studies reported the role of TLR7/8 to sense the presence of SARS-CoV-2 ssRNA and induction of MYD88 dependent NF- $\kappa$ B pathway activation and the release of pro-inflammatory cytokines from different cell lines (Campbell et al., 2021; Li et al., 2013; Salvi et al., 2021). Besides, the coding region of the E protein and ORF10 of SARS-CoV-2, enriched with CpG, thought to be recognized by TLR9 and subsequently elicit pathogenic hyperinflammatory responses, though further evidences need to clarify whether TLR9 directly detects viral components derived from SARS-CoV-2 (Bezemer and Garssen, 2021).

So, immediately after infection, the TLR pathway can be directly activated by either ligand induced conformational changes, or alternatively, by sensing of viral RNA in endosomal environment (Fig. 1). The ligand induced TLRs then interacts with adapter proteins to recruit catalytically active kinases that are able to initiate the activation of several downstream transcription factors (NF- $\kappa$ B, IRF-3, c-Jun N kinase, MAPK) upon catalysis of proximal proteins responsible for nuclear translocation and binding with targeted promoter. Therefore, the transcription of diverse genes occur that can either clear the viruses or in other instances create inflammatory stages with increasement of disease severity due to loss of regulation in upstream signaling pathways.

## 3. NF- $\kappa$ B pathway activity against SARS-CoV-2 infection

NF- $\kappa$ B is a crucial transcription factor that leads to the expression of diverse genes including inflammatory cytokines, chemokines, soluble factors, and enzymes for mounting immune response against pathogenic invasion of host cells, besides, regulating cell growth, apoptosis and other important cellular behaviors (Hiscott et al., 2001). However, uncontrolled activation of this pathway may cause different chronic diseases such as inflammatory diseases, cancers, mitochondrial and nervous system disorders (Shih et al., 2015).

Normally, in unstimulated cells, canonical NF- $\kappa$ B dimeric complex p65-p50 resides in the cytoplasm as an inactive form due to the inhibitory activity of I $\kappa$ B- $\alpha$ , a protein capable to mask the nuclear localization domain of the dimeric NF- $\kappa$ B protein complex, consequently, preventing the nuclear transportation and DNA binding ability of NF- $\kappa$ B (Santoro et al., 2003). This state of NF- $\kappa$ B sequestration in cytoplasm can be called as the inactivated form of NF- $\kappa$ B pathway.

The exposure of cells to a variety of stimuli including bacterial or viral antigens can induce IKK kinase complex activation. As a result, signal induced degradation of I $\kappa$ B- $\alpha$  occur through phosphorylation at Ser36 and Ser38 by IKK kinase and subsequent ubiquitination (Nishikori, 2005). The free NF- $\kappa$ B complex is then enter into the nucleus to bind with DNA and switch on the expression of specific genes that have important functions in controlling innate immune responses.

The NF- $\kappa$ B pathway provides an attractive target to the invading viral pathogens, as activation of NF- $\kappa$ B is a quick and immediate early event that occurs rapidly in response to a stimulatory agent without the requirement of de novo protein synthesis, and results in a strong transcriptional stimulation of several early viral genes in addition with cellular genes (Hiscott et al., 2001). The aberrant activation of NF- $\kappa$ B signaling can promote excessive cytokine or chemokine production and inflammatory cell recruitment, thereby causing excessive and/or chronic tissue damage and inflammation (Liu et al., 2017). Several viruses contain functionally important NF- $\kappa$ B-binding sites that cause abnormal activation of NF- $\kappa$ B pathway with induced pathogenesis

including HIV-1 (Hiscott et al., 2001), cytomegalovirus (DeMeritt et al., 2004), SV40 (Hiscott et al., 2001), hepatitis B virus (Su and Schneider, 1996), HSV1 (Rong et al., 1992), and Rotavirus (LaMonica et al., 2001). The emerging COVID-19 caused by SARS-CoV2 has become a major public health concerning issue due to the development of serious illness by causing innate and adaptive immune system disorder, cytokine storm, tissue damages, and systemic inflammation (Mueller et al., 2020). A remarkable level of IL-2, IL-6, IL-8, TNF- $\alpha$ , IFN- $\gamma$ , MCP-1, MIP-1 $\alpha$ , IP-10, and GM-CSF in patient's blood is a common clinical manifestation of COVID-19 severe cases (Huang et al., 2020b). Since the disease severity and death of COVID-19 patients is associated with elevated levels of inflammatory cytokine production, the role of activated NF- $\kappa$ B signaling by SARS-CoV-2 infection can be demonstrated.

Several recent studies reported the evidence of NF- $\kappa$ B pathway activation following SARS-CoV-2 infection either from clinical studies of COVID-19 cases or experimental data derived from in vitro infection. TLR induced NF- $\kappa$ B pathway activation by SARS-CoV-2 is quite common (Mabrey et al., 2021). RNA-sensing TLR-mediated NLRP3 inflammasome formation followed by NF- $\kappa$ B induction has already been reported (Campbell et al., 2021). Meanwhile, evidence also available on Spike protein mediated NF- $\kappa$ B activation upon TLR2 induction in either monocyte, macrophage and lung epithelial cell (Khan et al., 2021). Besides, angiotensin- II induced NF- $\kappa$ B pathway activation also suggested (Okamoto and Ichikawa, 2021). In addition, ORF7 mediated NF- $\kappa$ B pathway activation and pro-inflammatory cytokine production was reported (Su et al., 2021). NSP5 mediated activation of NF- $\kappa$ B pathway also reported by another group where the study proved that the protein can upregulate NF- $\kappa$ B dependent genes upon inducing the SUMOylation of Mitochondrial antiviral-signaling protein (MAVS) (Li et al., 2021).

### 3.1. ssRNA sensing by TLRs causes NF- $\kappa$ B pathway activation

We already mentioned in the earlier section that ssRNA of SARS-CoV-2 can be recognized by endosomal TLRs which have impact on NF- $\kappa$ B pathway activation in a MYD88 dependent manner. The role of TLR7, 8 and 9 in sensing SARS-CoV-2 ssRNA and induction of MYD88 dependent NF- $\kappa$ B pathway activation and release of pro-inflammatory cytokines in different cell lines has been suggested from several studies (Campbell et al., 2021; Li et al., 2013; Salvi et al., 2021). Campbell et al. (2021) showed that GU-rich RNA derived from spike protein of either SARS-CoV-2 and SARS-CoV-1 can induce TLR8 activation where the TLR8 act as a PRR or sensor of GU-rich viral RNA. The conformational change in the TLR8 followed by ligand induction can activate MYD88, the canonical adaptor for inflammatory signaling pathways downstream of the members of Toll-like receptor (TLR) and interleukin-1 (IL-1) receptor families (Deguine and Barton, 2014). Activated MYD88 then recruits the IKK or IL-1 receptor associated kinases, leading to the nuclear translocation of NF- $\kappa$ B transcription factors. As a result, transcription of numerous proinflammatory mediators including IL-6, IL-12, IL-27, TNF- $\alpha$ , IFN- $\gamma$ , and IL-1 $\beta$  initiate (Akira et al., 2001, 2006). It has been found that macrophage treated with GU-rich RNA of SARS-CoV-2 can significantly induce the release of IL-1 $\beta$ , IL-6, TNF- $\alpha$  in the cell supernatant in comparison with either SARS-CoV-1 or HIV-1 (Campbell et al., 2021).

### 3.2. Spike protein induced NF- $\kappa$ B activation

It is quite common that spike protein of SARS-CoV-2 can recognize cell surface TLRs and subsequently promote inflammatory cytokine release followed by NF- $\kappa$ B pathway activation. A study conducted by Khan et al. (2021) showed that either S1 or S2 subunit of S protein can potentially induce the expression of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , CXCL1 and CXCL2 in macrophages, monocytes and epithelial cells. Most importantly, the study also showed that S protein expressing epithelial cell infected with SARS-CoV2 can stimulate macrophages and monocytes to

produce inflammatory mediators in a paracrine manner. MYD88 is an adapter protein that has involvement with the activation of either NF- $\kappa$ B pathway and MAPK pathway following the TLR recognition of PAMPs or viral protein. Functional analysis in bone marrow derived macrophages (BMDM) deficient with MYD88 has come out with the observation that S protein-mediated activation of the NF- $\kappa$ B pathway involves TLR/MYD88 signaling event. This finding was confirmed in MYD88 deficient cells which fail to express the proinflammatory cytokines or chemokines in compare with MYD88 expressing cells. To further confirm, the study performed another round of experiment with either TLR2 and TLR4 deficient macrophages, the two most potent receptors for sensing lipid based antigenic substances. The finding has come out with no activation of the NF- $\kappa$ B pathway in Tlr2-/- BMDM, while activation of this pathway was unaffected in Tlr4-/- macrophages upon stimulation with S2 subunit of S protein. The study concluded that SARS-CoV-2 Spike protein is a potent viral PAMP that activates the NF- $\kappa$ B pathway upon recognized by TLR2, leading to the expression of inflammatory mediators in innate immune and epithelial cells.

### 3.3. ORF7 mediated NF- $\kappa$ B activation

ORF7a is an accessory protein of SARS-CoV-2 and SARS-CoV-1 that has strong activity in controlling different cell signaling pathways. The protein has a structural homology with Intracellular adhesion molecule 1 (ICAM-1) which binds to the T lymphocyte integrin receptor LFA-1 (Nizamudeen et al., 2021). Earlier studies showed that SARS-CoV-1 accessory proteins ORF3a, M, ORF7a, and N proteins can upregulate NF- $\kappa$ B activity (Liao et al., 2005; Zhang et al., 2007). A recent study also confirms the similar activity of this protein in SARS-CoV-2, though ORF7a has found to be more potent in such activities in comparison with other accessory protein (Su et al., 2021). Upon luciferase reporter assay the study confirmed that ORF7a of SARS-CoV-2 significantly induce the promoter responsible for NF- $\kappa$ B pathway activation and increases proinflammatory cytokine expressions regardless of different cell types. As the evidence of NF- $\kappa$ B activation is pronounced with the nuclear translocation of NF- $\kappa$ B dimeric subunits, p65-p50, the study further confirms from subcellular distribution that 85% of the cells stimulated with ORF7a were expressing p65 in nucleus. The expression of NF- $\kappa$ B mediated pro-inflammatory cytokines and chemokines especially IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ , CXCL9, CXCL21 were highly expressed upon stimulation with ORF7a, implicating a strong role of the protein in disease severity due to activation of NF- $\kappa$ B pathway.

### 3.4. NSP14 triggers NF- $\kappa$ B pathway

Nsp14 is a conserved, multifunctional, and non-structural viral factor required for efficient viral replication upon participation in synthesizing and modifying coronaviral sub-genomic RNA (Ma et al., 2015). Though earlier studies illustrated that Nsp14 suppresses Type 1 IFN signaling and nuclear translocation of IRF3 to facilitate viral invasion of the host's antiviral immune responses (Yuen et al., 2020), recent evidence suggested that the protein can participate in NF- $\kappa$ B pathway activation (Li et al., 2021). As the protein can express at earlier stage of primary viral infection, it may activate NF- $\kappa$ B signaling so the virus can continue replication and spread newer infection to the neighboring cells. Li et al. (2021) identified that Nsp14 increases nuclear translocation of NF- $\kappa$ B protein p65 and induces upregulation of downstream cytokines, such as IL-6 and IL-8, which have also been detected in lung tissues of COVID-19 patients and SARS-CoV-2 infected animal model (Leng et al., 2020). Besides, the study of Li et al. (2021) identified that nsp14 can mediate the pathway induction upon associating with host inosine-5'-monophosphate dehydrogenase 2 (IMPDH2) protein. Both genetic knock down and chemical inhibition experiment confirmed that IMPDH2-NSP14 interaction is essential for NF- $\kappa$ B pathway activation following the viral infection.



### 3.5. NSP5 induces NF- $\kappa$ B pathway upon SUMOylation of MAVS

Meanwhile, Li et al. (2021) showed that NSP5 of SARS-CoV-2 can induce the upregulation of several pro-inflammatory cytokines, especially, IL-6, IL-1 $\beta$ , TNF- $\alpha$ , IL-2 in THP-1 and calu-3 cells. Further analysis showed that the protein can upregulate these cytokines by activating NF- $\kappa$ B pathway upon inducing the SUMOylation of MAVS.

### 4. TRIF-IFN pathway

As described in the earlier section, induction of the TLR associated MYD88 is associated with NF- $\kappa$ B pathway activation, while TIR-domain-containing adaptor-inducing IFN- $\beta$  (TRIF) pathway leads to IFN production. The usual cellular responses connected with IFN production involves: TLR3/4 sensing of viral components can cause conformational change in the PRR, which is then able to recruit TRIF and proximal kinases responsible for IRF3 activation. The activated IRF3 then translocate into the nucleus and bind with IFN promoter, thus IFN production occur (Kawasaki and Kawai, 2014). Though the antiviral properties of TLR induced type I and type III IFN are critical for coordinated viral control and clearance, dysregulated IFN response assumed to have a role in COVID-19 disease severity (Acharya et al., 2020; Mabrey et al., 2021).

Earlier studies showed that in TRIF knock out mouse model, the infection of mice with SARS-CoV could induce robust generation of inflammatory cytokine with higher load of virus similar to either TLR4 or TRAM knock out mice (Totura et al., 2015). This finding suggested that lack of IFN could give chance to higher virus replication, while MYD88 dependent pathways may continue to produce cytokines (Mabrey et al., 2021; Totura et al., 2015). A number of reports on COVID-19 studies showed that SARS-CoV-2 infection induces a limited IFN production which was confirmed from the peripheral blood or lung of severe COVID-19 patients unlike pathogenic Influenza infection (Acharya et al., 2020; Blanco-Melo et al., 2020; Hadjadj et al., 2020). There are multiple reports on SARS-CoV-2 mediated inhibition of IFN signaling and blocking of proximal molecules associated with the IFN production (Kim and Shin, 2021; Wu et al., 2021). Several earlier reports on SARS-CoV and MERS-CoV showed that delayed or minimal IFN responses led to the accumulation of highly activated macrophages in the lung that could induce immunopathology, enhanced the recruitment of neutrophils to the lungs, depletion and functional exhaustion of NK cells, as well as impaired T cell Responses (Channappanavar et al., 2016; Zheng et al., 2021). The limited IFNs with unlimited production of pro-inflammatory cytokines and chemokine during SARS-CoV-2 infection suggests robust activation of NF- $\kappa$ B but not that of IFN-regulatory factor 3 (IRF3) and IRF7 (Acharya et al., 2020; Mabrey et al., 2021). Due to the loss of net balance in either NF- $\kappa$ B or IFN signaling, a severe form of immunopathological condition arise that fails to clear the virus effectively.

However, some reports on COVID-19 claimed that type 2 IFN (e.g., IFN- $\gamma$ ) levels increase upon SARS-CoV-2 infection. A study by Liu et al. (2021) found that elevated levels of IFN- $\gamma$  were associated with greater viral load and lung damage in COVID-19. Another report by Huang et al. (2020a) observed an increasing level of IFN- $\gamma$  in COVID-19 patients in compare to healthy individuals. Moreover, lung tissue of COVID-19 patients also reported to contain IFN- $\gamma$  in higher levels (Chu et al., 2020).

### 5. NF- $\kappa$ B activation crosstalks in NLRP3 inflammasome formation

Though NLRP3 (NLR family pyrin domain containing 3) inflammasome is an important arm of host immune defense against different viruses, dysregulation of the events associated with its activation (due to upstream NF- $\kappa$ B pathway) can trigger the pathogenesis of several inflammatory disorders, with a clinical outcome of alveolar damage, pulmonary fibrinolysis and injury, acute respiratory disease syndrome with massive cell death by pyroptosis (Amin et al., 2022). During NLRP3

inflammasome formation, upstream NF- $\kappa$ B pathway usually acts as a priming step that causes the transcription of several pro-inflammatory genes including IL-1 family of cytokines followed by TLR-MYD88 induction. The second signal of catalytic caspase-1 formation comes from oxidative stress, which formed from virally or environmentally induced damage molecules such as ROS, mtDNA, LPS etc., (Amin et al., 2022; de Rivero Vaccari et al., 2020).

Besides catalyzing IL-1 family of pro-inflammatory cytokines, caspase-1 can also cleave gasdermin D (GSDMD) into active form, a pore-forming substance that cause programmed cell death in the form of pyroptosis (Rodrigues et al., 2021). The pore-forming activity of the N-terminal cleavage product of GSDMD induces cell swelling and lysis, as a result, the release of cytoplasmic contents (containing inflammatory cytokines) into the extracellular space occur that further recruit and activate different immune cells to the site of infection (Liu et al., 2021). Infiltrated immune cells (macrophages, neutrophils) subsequently accelerate inflammatory reactions with severe lung damage and organ disorders. There are multiple reports on NLRP3 inflammasome induced COVID-19 severity and increased pathological symptoms. Rodrigues et al. (2021) found that SARS-CoV-2 infected monocytes and peripheral blood mononuclear cells (PBMC) isolated from healthy donors could accelerate cell death followed by inflammasome formation. The evidence of active inflammasome specks were detected from the postmortem lung sections of COVID-19 patients (Ferreira et al., 2021; Rodrigues et al., 2021; Toldo et al., 2021). Ferreira et al. (2021) reported that SARS-CoV-2 infection can engage inflammasome in human monocytes and triggers pyroptosis in both experimental infection and clinical samples derived from patients under intensive care. Moreover, SARS-CoV-2 infected lung epithelial cells reported to induce caspase-8 activation, promote cell apoptosis upon processing of proinflammatory cytokine, especially, pro-IL-1 $\beta$  into the bioactive form (Li et al., 2020). Fig. 1 highlights the dysregulated cell signaling events and resulting adverse consequences in a SARS-CoV-2 infected cell.

### 6. Underlying immune components involved with dysregulated cell signaling

Owing to the impact on physiologic changes and genetics, several underlying cellular conditions are associated with the dysregulation of cell signaling events followed by SARS-CoV-2 infection.

#### 6.1. Telomere shortening

A telomere is a region of noncoding DNA comprising tandem repeats of TTAGGG at the end of linear chromosomes attached with specialized protein and provide genetic stability and proper cell functioning (Ruiz et al., 2022). During the normal process of DNA replication in somatic cell division, the length of telomere tends to decrease gradually that causes a progressive telomere shortening (TS) with advancing of age (Ruiz et al., 2022). The progressive shortening of telomere reaches a dysfunctional state in aged individuals with impaired host response to cellular stress, inflammatory responses and mitochondrial defective function (Lara et al., 2020). It has been reported that mice with defective telomere have mitochondrial abnormalities, oxidative stress, and hyperactivation of the NLRP3 inflammasome (Kang et al., 2018). Telomere dysfunction causes the p53-mediated cellular responses such as repression of peroxisome proliferator-activated receptor gamma coactivators (PGCs) that are major regulators of mitochondrial physiology and metabolism (Kang et al., 2018). Such p53-PGC axis, resulted from dysfunctional telomere is associated with abnormal mitochondrial function, decreased gluconeogenesis, increased reactive oxygen species (ROS). The increased ROS can be a potential DMAP or priming component of NF- $\kappa$ B activation or NLRP3 inflammasome formation that can subsequently contribute to organ or metabolic failure and inflammatory reactions (Table 1).

**Table 1**  
Potential biomarkers associated with severe COVID-19.

Biosignature	Signaling pathway	Activity in COVID-19
IL-6	MAPK, JAK-STAT, P13-K, NF-κB	Induce CRP level, affect the T cell function, promote immune cell recruitment to the site of inflammation, triggers pro-inflammatory reactions, induce cytokine storm (Costela-Ruiz et al., 2020).
IL-1	MAPK, NF-κB, NLRP3	Elevated level of IL-1β and IL-18 induce cytokine storm in COVID-19, associated with increased viral load, loss of pulmonary function, lung damage, and mortality risk (Campbell et al., 2021; Rodrigues et al., 2021; Vora et al., 2021).
TNF-α	NF-κB pathway, MAPK pathway	Elevated level in serum correlate with the increase of COVID-19 severity, cytokine storm, associated with poor prognosis (Huang et al., 2020a).
GSDMD-D-N	NLR-	Induce pyroptosis in COVID-19 patients, triggers massive cell death by releasing inflammatory molecules to extracellular space (Rodrigues et al., 2021).
Caspase-1	NLR-	Promote COVID-19 severity and pathogenesis by inducing the catalysis of pro-IL-1 to mature IL-1, and inactive GSDMD to active GSDMD-N (Ferreira et al., 2021).

### 6.2. Neutrophil activity and NETs formation

An elevated neutrophil count is correlated with COVID-19 severity. This correlation of high neutrophil count is confirmed by the remarkable detection of RETN, HGF, and LCN2 (typical marker of neutrophils) from severe COVID-19 patient sera (Meizlish et al., 2021). Though the ability of neutrophils to generate NETs (extracellular neutrophil traps) in response to any viral infection play a beneficial role in the defense of its host from pathogens, excessive inflammation may cause a cascade of unfavorable reactions such as autoimmunization, damage to surrounding tissue, or the occurrence of atherothrombosis (Janiuk et al., 2021). The NETs formation can give rise to inflammatory responses and disease progression by affecting the circulatory system with disseminated intravascular coagulation, hypertension, and venous thromboembolism (Arcanjo et al., 2020; Janiuk et al., 2021; Mozzini and Girelli, 2020; Thierry and Roch, 2020). The Neutrophil elastase, high levels of cfDNA (circulating free DNA), histones, high blood levels of D-dimers (as dissolved clots), and higher levels of calprotectin (a neutrophil activation marker) are several reported indicators associated with NETs formation that have significant correlation with the progression of COVID-19 (Janiuk et al., 2021).

### 6.3. Mitochondrial dysfunction and oxidative stress

Mitochondria plays a crucial role in maintaining cellular homeostasis by regulating the balance of calcium levels, redox status, autophagy, apoptosis, inflammation and programmed cell death (Mishra et al., 2021). The dysfunction of mitochondria by viral infection can create an imbalance in electron transport system that causes overproduction of mtROS. The overproduced ROS can thus stimulate NLRP3 inflammasome induced IL-1 related protein expression upon enhancing the release of mtDNA into the cytosol. It has been found that SARS-CoV-2 infection can disrupt Ca<sup>2+</sup> ion channel activity that have an influence in triggering the formation of PTP complex, upregulation of SPG7 and thus affect host-mitochondrial bioenergetics (Ramachandran et al., 2022). Recent evidence showed that SARS-CoV-2 infected leukocytes can enhance the mitochondrial ROS production followed by mitochondrial dysfunction that induce cell death in COVID-19 patients (De la Cruz-Enríquez et al., 2021). Collectively, the combination of hindered respiration, impaired ATP production, elevated ROS generation, and reduced detoxification capacity with abnormal immune functions likely play pivotal role in the increase of inflammation and severity of

COVID-19 (De la Cruz-Enríquez et al., 2021; Dutta et al., 2020). Recent evidence from De la Cruz-Enríquez et al. (2021) proved that mitochondrial dysfunction, metabolic alterations with increased glycolysis, and high levels of mitokine in PBMCs from patients with COVID-19 are associated with increased disease severity. Notably, the study showed that significantly reduced ATP-linked respiration, reserve capacity, and maximal respiration are associated with compromised mitochondrial functions against SARS-CoV-2 infection.

### 6.4. Decreased naive T cell production

The recognition of a new antigen unfamiliar to the immune systems and production of proper immune response by a balanced activation of signaling molecules requires continual production of naive T cell. It has been found that infection of the newly evolved SARS-CoV-2 and resulting disease severity is more clearly pronounced in people that have undergone a stage (e.g. advanced age people) with impairment in naive T cell production (Mueller et al., 2020). The reduced capacity of naive T cell production enhances SARS-CoV-2 infection and replication, odds on promoting uncontrolled cytokine production and clinical illness severity (Schwartz et al., 2020).

### 6.5. Impaired adipocyte function

The function of normal adipocyte is to act as a calorie storage system by accepting chemical energy in the form of glucose and fatty acid from the blood during lipogenesis. This activity of adipocyte can be impaired in patients with hyperplasia or hypertrophy that can promote the formation of ceramides and cholesterol crystals. The produced crystals can activate tissue resident macrophage upon TLR4 signaling which has a positive impact in triggering ROS production, as well as IL-6 and TNF-α release- the two most pro-inflammatory products of NF-κB pathway stimulation (López-Reyes et al., 2020; Lee et al., 2001). The activated NF-κB pathway can act as a priming step for NLRP3 inflammasome formation, subsequently inflammatory IL-1 family of cytokines release is induced by the binding of ceramides, fatty acids, oxidized low-density lipoproteins and cholesterol crystals to TLR 2/4 (López-Reyes et al., 2020). Moreover, in our previous study we reviewed several studies on the positive correlation of obesity with COVID-19 severity under abnormal immunological conditions (Amin et al., 2022).

### 6.6. Hyperglycemia and glyco-lipotoxicity

The products of intermediate metabolism such as urate, ceramides, cholesterol crystals, extracellular ATP and amyloid peptides formed from hyperglycemia and glyco-lipotoxicity can serve as potential DAMPs in inflammasome formation and subsequent production of caspase-1 and IL-1 cytokines (Lambadiari et al., 2020).

In addition to the aforementioned immune components, other conditions that can induce dysregulated immunity in COVID-19 include: prolonged monocyte activation, defects in TLR, Thymus involution, abnormal state of ACE2 expression that can accelerate abnormal signaling molecules induction and create excessive inflammation other than providing proper immune response (Mueller et al., 2020). It is worth noting that aging, obesity, compromise immune system, diabetes and other underlying health disorders are the major reasons behind the formation of these pathological DAMPs.

## 7. Clinical features of COVID-19 resulted from dysregulated cell signaling pathways

### 7.1. Respiratory symptoms

The major symptoms of COVID-19 respiratory complications have been observed as pneumonia, hypoxia, lung edema manifested as ALI and ARDS that can lead to lung failure in most cases (Morris et al., 2021;

Tian et al., 2020). The major pathological changes observed in such patients are - diffuse alveolar damage, increased epithelial and endothelial cell permeability, leakage of fluid into the pulmonary interstitium, and significant disruption of gas exchange. The development of these conditions is largely associated with the production of some common inflammatory cytokines such as IL-1 $\beta$ , IL-18, IL-6, IL-8, TNF- $\alpha$  (Zhao et al., 2021a). The incident of ARDS can be promoted by the infiltration of vascular endothelial cells, platelets, and neutrophils with excessive production of neutrophil extracellular traps (NETs) that can promote the development of ALI and ARDS (Frantzeskaki et al., 2017; Zhao et al., 2021a).

### 7.2. Neurological symptoms

The most noticeable neurological symptoms in COVID-19 are anosmia, ageusia, and headache, with a further possible association with stroke, impairment of consciousness, seizure, and encephalopathy (Asadi-Pooya and Simani, 2020). The ability of SARS-CoV-2 to affect human nerve cells (eg. neural progenitor cells and brain organoids) raising the possibility that the virus can cross the Blood brain barrier (BBB) and enter the CNS via neuro-invasion (Zhang et al., 2020). A report by Almutairi et al. (2021) described that IL-1 $\beta$  and IL-6 can stimulate neuroinflammation by passing through the BBB which can promote the permeation of virus-infected peripheral white blood cells and monocytes.

### 7.3. Cardiovascular symptoms

The expression of ACE2 receptor in heart cells can increase the recruitment of adapter proteins involved with the activation of inflammatory signaling pathways upon SARS-CoV-2 infection that may trigger the production of inflammatory cytokines (Iqbal et al., 2020; Zhao et al., 2021a). As a result, different cardiac disorders arise such as myocarditis, failure of contractile function, damage to cardiomyocytes and release of cardiac injury markers that can further lead to ischemia, vascular inflammation, coagulation and thrombosis (Colliva et al., 2020). Recently, Hoel et al. (2021) found an elevated level of lipid binding protein, LBP in the plasma of COVID-19 patients with cardiac dysfunction. The high level of LBP was correlated with elevated level of IL-18, IL-18BP and IL-1Ra in those patients, suggesting gut leakage of LPS and subsequent inflammasome activation with a potential gut-heart axis in COVID-19 (Hoel et al., 2021). Meanwhile, Ramachandran et al. (2022) showed that SARS-CoV-2 infection triggers mitochondrial PTP (permeability transition pore) complex activity, alter mitochondrial morphology and function, disrupt Ca<sup>2+</sup> cycling, thus induce cardiomyocyte damage and the development of heart failure.

### 7.4. Renal dysfunction

SARS-CoV-2 infection has been also reported to affect kidney function and causes acute kidney injury (AKI) (Ahmed et al., 2020). AKI has been reported as a significant problem in hospital administered patients with severe COVID-19 (ARDS or on mechanical ventilation, as well as in patients with hypertension or diabetes) (Gabarre et al., 2020). The virus infection in kidney thought to activate TLR4 mRNA in tubular cells that promote tubular necrosis, ischemia, inflammation, and injury though there is no direct evidence with SARS-CoV-2 yet (Manik and Singh, 2021). The expression of ACE2 on kidney, platelets adhesion along with fibrin in peritubular capillaries, complement induced neutrophil attraction, TLR induction or NLRP3 inflammasome formation are several reasons that make kidney a direct target site for developing SARS-CoV-2 related pathogenesis (de Rivero Vaccari et al., 2020; Manik and Singh, 2021).

### 7.5. Gastrointestinal disorders

Common gastrointestinal disorders such as vomiting, loss of appetite, abdominal pain accompanied by diarrhea has been noticed in COVID-19 patients even in the absence of any respiratory symptoms. The ionic imbalance associated with SARS-CoV-2 infection can be a possible reason for inflammasome activation in the gut and associated disorders (Prasad, 2021). Besides, an alteration in gut-lung axis due to SARS-CoV-2 binding with ACE2 can also possibly affect the normal microbial flora in gut, thus gastrointestinal disorders arise subsequently (de Rivero Vaccari et al., 2020).

## 8. Major biomarkers of abnormal cell signaling events

The common mediators of immune system that have been constantly detected in COVID-19 cases can be categorized as potential biomarkers of abnormal cell signaling.

**IL-6:** The level of IL-6 has been reported to have a correlation with virus titer in serum (Manik and Singh, 2021). Elevated level of IL-6 seems to induce CRP level with a disruption in the T cell function, decline the production of albumin, fibronectin and transferrin (Costela-Ruiz et al., 2020; Herold et al., 2020). Besides, the overproduction of this cytokine is observed with poor prognosis of the disease (Wan et al., 2020). The transcription and synthesis of IL-6 is mainly regulated by upstream NF- $\kappa$ B pathway and downstream NLRP3 inflammasome formation in most instances.

**TNF- $\alpha$ :** The serum level of TNF- $\alpha$  are abnormally high in COVID-19 severe cases that have pro-inflammatory effects in functioning (Manik and Singh, 2021). The poor prognosis of COVID-19 thought to have a correlation with the rising level of this cytokine in serum similar to SARS and MERS (Costela-Ruiz et al., 2020; Huang et al., 2020a).

**IL-1:** The major inflammatory cytokines released by inflammasome activation followed by NF- $\kappa$ B induction are IL-1 family of cytokines. The increasing level of IL-1 (especially IL-1 $\beta$ , IL-18) has a significant correlation with COVID-19 severity (Rodrigues et al., 2021). Though the detection of IL-1 $\beta$  can be an excellent biomarker for severe COVID-19, the short half-life of the molecule makes it difficult to measure in some instances. However, as an alternate, a surrogate of IL-1 $\beta$ , IL-1Ra is a frequently suggested marker since, it can be consistently detected in severe COVID-19 (Ferreira et al., 2021; Vora et al., 2021).

**Caspase-1:** Caspase-1 is an evolutionary conserved enzyme that can interact with caspase activation and recruitment domain (CARD) containing proteins such as apoptosis-associated speck-like protein containing a CARD (ASC) and nod-like receptor (NLR) family of proteins through CARD-CARD interactions in the formation of inflammasomes (Mariathasan et al., 2004). The proteolytically activated caspase-1 known as Casp1p20 has been constantly detected in COVID-19 patients serum and SARS-CoV-2 infected monocytes and macrophages that promote the activation of substrates, including the inflammatory cytokines IL-1 $\beta$  and IL-18 and gasdermin-D (Rodrigues et al., 2021). Therefore, the detection of activated caspase-1 is an important biomarker in severe COVID-19.

**LDH:** The damage in cell causes the release of lactate dehydrogenase, which is considered as a potential marker of vascular permeability in immune-mediated lung injury. The elevated lactate dehydrogenase (LDH) values were associated with several fold increased odds of severe COVID-19 disease (Szarpak et al., 2020).

**Inflammasome specks:** The recruitment and activation of procaspase-1 is promoted by the formation of ASC specks which can trigger the pyroptotic inflammatory cell death and pro-inflammatory cytokine release. However, the adapter protein ASC can function as a bridge between different sensory receptors notably NLR, the oligomerization of which can promote ASC binding to large filaments that aggregate into large structures known as ASC specks (Vora et al., 2021). The formation of this speck is essential for interaction with pro-caspase zymogen to catalyze pro-inflammatory cytokines (Soriano-Teruel et al.,



2021). Therefore, identification of inflammasome specks in blood monocytes and lung section of severe COVID-19 patients can be one of the important markers of inflammasome formation in addition to pyroptosis.

**GSDMD:** Activated caspase-1 can cleave gasdermin D (GSDM-D) at the linker region between the amino (N) and carboxy (C) terminus, resulting in the release of the N-terminus fragment from the C-terminus (Broz and Dixit, 2016). The N-terminus GSDM-D is capable of inducing pore formation in the cell membrane, with the subsequent release of inflammatory molecules into outside environment, thus severe inflammatory disorders arise with massive cell death (de Rivero Vaccari et al., 2020; Rodrigues et al., 2021). Therefore, detection of GSDM-D-N could be a potential biosignature for assuring cell death and severe clinical conditions in COVID-19.

**LPS:** The detection of LPS in the plasma of COVID-19 patients is quite common as secondary bacterial infection can be occurred in SARS-CoV2 infected lung. The LPS has the potency to induce TLRs and downstream NF- $\kappa$ B pathway activation (Huber et al., 2018). Report showed that high lipopolysaccharide (LPS) levels in the circulation has a correlation with severity of COVID-19 since the LPS has been seen to interact with SARS-CoV-2 spike protein and boost the inflammatory responses (Petruk et al., 2020). So, the detection of LPS could be considered a useful biomarker in severe COVID-19 patients.

**Abnormal Cell count:** Low count of lymphocytes and thrombocytes, while increasing level of neutrophils is common phenomenon in severe COVID-19 patients (Manik and Singh, 2021).

**CRP:** C-reactive protein is a non-specific acute phase protein produced by hepatocytes that can increase in response to infection and inflammation, thus it become a biomarker for confirming different viral or bacterial infection (Thompson et al., 1999). In COVID-19 diagnostics, CRP also has been suggested inconsistently as a prognostic marker, since, elevated level of CRP for patients with COVID-19 was associated with increased inpatient mortality and was indicative of disease severity at admission (Stringer et al., 2021).

**Others:** Elevated level of D-dimer, a fibrin degradation product has been constantly detected in COVID-19 cases in severe stage. Besides, increasing level of creatinine, an indication of kidney infection also reported to found in patients with COVID-19.

## 9. Concluding remarks and perspectives

Responding to SARS-CoV-2 infection, TLRs and their proximal accessory components and adapters become activate in a natural host-antiviral defense manner. However, hyper-inflammation accompanied by septic shock, acute lung injury, acute respiratory distress syndrome and the organ damage has been observed under TLR induced NF- $\kappa$ B, MAPK, NLR pathways and in some instances downregulation of TRIF-induced IRF3 pathway upon SARS-CoV-2 infection in most of the severe COVID-19 cases. Hence, we could hypothesize that in spite of protective function in immunity, a loss of balance in cell signaling events could accelerate excessive inflammation due to dysregulated activation of NF- $\kappa$ B, mostly upon TLR-MYD88 induction, whereas, a limited and delayed TRIF-IFN induction seems to support increased viral replication. Moreover, in addition with upstream signaling dysregulation, the evidence of inflammasome specks formation and inflammasome induced severe pathophysiology suggests a dysfunctional immunological state of those patients whose immune system are pre-occupied by mitochondrial damage, telomere shortening, impaired adipocyte function, abnormal neutrophil activities and so on. Therefore, strategies should be taken by considering either the physiological and immunological state of the patients and stage of the disease to compensate the abnormalities. The selection of therapeutics should consider not only to antagonize the downstream soluble mediators (IL-6, IL-1 or other cytokine), but also to counteract upstream pathways by targeting potential TLRs that have direct interaction with the PAMPs or suppress the nuclear translocation of cytoplasmic transcription factors especially NF- $\kappa$ B. However, more

detailed analysis is still needed to understand the impact of TLRs or proximal accessory signaling molecules in response to SARS-CoV-2 infection and pathogenesis.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

## Data availability

Data will be made available on request.

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