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RESEARCH PAPER

Mechanism of Innate Immune Responses Against SARS-COV-2 Infection

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A B S T R A C T:
The immunopathogenesis of Coronaviruses (CoVs) is still under study. The innate immunity components can differentiate self and non-self-antigens, help viral particle recognition, and restrict viral replication by producing antiviral proteins. Induction of antiviral innate immune responses against SARS CoV-2 commonly depends on recognizing pathogen-associated molecular pattern molecules (PAMPs) by pattern recognition receptors (PRRs). PAMPs mount the activation of Toll-Like Receptors (TLR) cascade and initiate transcription factors, involving Nuclear Factor- κB (NF-Kb), Interferon Regulatory Factors (IRF3), and (IRF7), which results in the synthesize of Interferons (IFN) type I Subsequently, type I IFN inhibits viral replications, regulates, and modulates the immune system. Dendritic cells (DCs) reside in the respiratory tract. They can recognize viral particles via TLR and initiate innate and adaptive immunity and repress viral spreads through IFN production. barrier of TLR, impediment of IFN expression, and/or lack of innate immune responses may be associated with tissue destruction after viral elimination. Here, emerging the reviews knowledge on the mechanism of non-specific immune responses against SARS-COV-2.

KEY WORDS: Fr Keywords: Coronavirus; Toll-like Receptors; Type I Interferons; Dendritic cells, Innate Immunity.
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1.INTRODUCTION:

Respiratory tract infections represent a considerable high threat and cause significant morbidity and mortality rates worldwide, especially emerging pathogens such as influenza virus type A and Coronavirus (CoVs), which have caused minor to significant outbreaks of viral pneumonia worldwide (Perlman, 1998, Gillim-Ross and Subbarao, 2006).

The first person with CoV was diagnosed and identified on December 26, 2019. The epidemiological study revealed that the proposed outbreak was linked to a seafood market in Wuhan, Hubei province, China, by a newly emerged strain from the family of CoVs that causes respiratory illness, this CoV called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (Wu et al., 2020a). The whole RNA sequence of the virus was analyzed by phylogenetic analysis, and it is revealed that the virus is closely related to SARS-CoV (Wu et al., 2020b). The new study reported that phylogenetic tree analysis of structural proteins is highly linked to human SARS-CoV received in various countries, particularly such strains isolated from China (Dimonte et al., 2020).

Coronavirus has a large enveloped plus single-stranded RNA and is ball-shaped with a proximal 80-120 nm in diameter(Zhou et al., 2020). It comprises a lipid membrane with 3 or 4 glycoproteins (E), and a nucleocapsid (N). The spike protein (S), is responsible for attaching to the host-specific cell receptors (ACE2). Both

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Membranes (M) and (E) are integral proteins that are necessary for Coronavirus maturation (Carabelli et al., 2023). The nucleocapsid (N) forms a protective shell that helps in the packaging of the viral genome, and it is also believed to have a participation in RNA duplication and transcription (Vennema et al., 1996, Peiris et al., 2003, Kuo and Masters, 2002, Bosch et al., 2004).

Furthermore, other respiratory viruses such as avian flu (H5N1) and CoVs (SARS-CoV, MERS-CoV, and SARS-CoV-2) represents a continual risk for public health globally (Blbas et al., 2021). It is crucially important to understand virus-dependent mechanisms and host-dependent immune responses which may determine the severity of respiratory infections, also, it is essential in the avoidance and treatment of viral respiratory tract diseases (Prompetchara et al., 2020).

Host immune responses of both specific and non-specific types are triggered following viral infections, which is crucially required for infection clearance (Tirelli et al., 2023). In many cases, immunopathogenesis is associated with uncontrollable immune responses, resulting in pulmonary tissue damage, as during SARS-CoV infection, the epithelial cells of bronchi and alveoli are destructed by macrophages and neutrophils due to the secretion of pro-inflammatory cytokines (Interleukin-6), which contribute to inflammation and eventually death of the infected and uninfected cells by synthesizing toxic agents like oxygen species radical (Fraser et al., 2023, Ahmad et al., 2016). As tissue destruction, both hyper-activation and immunosuppression may occur, which affect viral elimination (Dandekar and Perlman, 2005).

2. INNATE IMMUNE RESPONSES

The innate immune system is one of the primary lines of the immune reaction (Varga et al., 2019). The mitochondria participate in a wide range of innate immune response pathways, acting as signaling platforms and sharing effector reactions (Figure 1) after cellular damage; thus, mitochondria seem to work as central hubs in the innate immune system (West et al., 2011).

The SARS-CoV-2 uses its essential proteins to pick up entrance into the host cell cytosol just as stifle signaling pathways, particularly with the Toll-like receptors (TLR) (Weiss and Navas-Martin, 2005, Al-Zahrani, 2021). For the most part, the interaction occurs between the viral RNA with TLR7 and TLR3. This cooperation starts a signal cascade, including the transcriptional factors IRF3 and NFkB (Mukherjee et al., 2019). These factors are additionally translocated into the nuclei, activating of signal transduction of pro-inflammatory cytokines and interferons (Wu et al., 2020b). IFN, thus, activates the JAK-STAT pathway through the phosphorylation of STAT-1 and -2. The familiar types of STAT-1 and -2 form additional structure buildings with IRF9 with the immediate arrival of dynamic IFN animating qualities (ISGs), bringing about massive concealment of viral duplications (Song et al., 2019, Mariani et al., 2019).

Several new studies note that SARS-CoV and SARS-CoV-2 target the same receptor of angiotensin-converting enzyme 2 (ACE2) for binding and entry into alveolar cells. Moreover, MERS-CoV identifies dipeptidyl peptidase-4 (DPP-4) as a specific receptor target (Zhu et al., 2020, Zhou et al., 2020).

Activation of the innate immune response to the viral infection massively depends on the recognition of viral particles by Pattern Recognition Receptors (PRRs), such as Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) (Hayden et al., 2006, Kerrigan and Brown, 2010). TLRs stimulate the production of IFN following activating the TLR cascade by PAMPs (Xagorari and Chlichlia, 2008).

2.1. PATHOGEN RECOGNITION RECEPTORS

2.1.1. TOLL-LIKE RECEPTORS

Toll-like receptors are transmembrane proteins type I that are associated with innate immunity. Cells of innate immunity recognize through

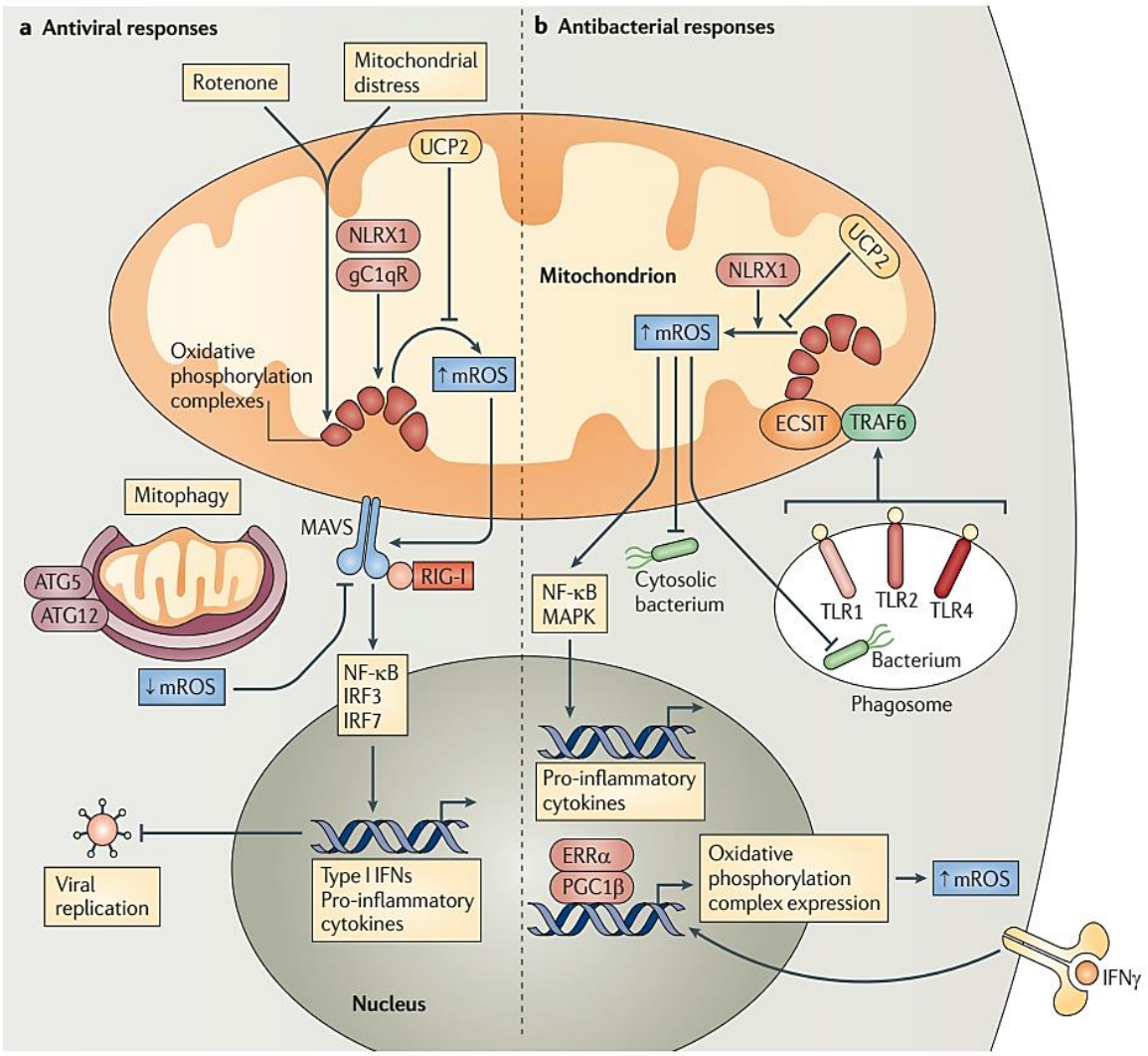

Figure 1. Mitochondrial reactive oxygen species and innate immune responses illustrating a/antiviral responses b/ antibacterial responses adapted from (West *et al.*, 2011).

microbial infections, particularly the viral ones, PAMPs, which trigger intracellular signaling pathways and switching gene expression (Kiziltaş, 2016).

The variety of TLRs can recognize different PAMPs. For instance, TLR3 detects dsRNA and viral products, while TLR9 recognizes unmethylated CpG in the genome of viruses (Xagorari and Chlichlia, 2008). A tiny synthetic altered immune molecule, including imiquimod, R-848, loxoribine, and bropirimine, is detected by TLR7. The expression of TLR7 and TLR9 by dendritic cells (DCs) is in the response of TLR7 and TLR9 ligands, then synthesizing a bulk of IFN such as IFNα and IFNβ and other pro-inflammatory cytokines (Akira and Hemmi, 2003). The research done by Diebold et al (2004) reported that inside the endosomes of alveolar macrophages, the viruses promote the forming of superoxide mediated by an enzyme known as NOX2-dependent NADPH oxidase with the aid of TLR7; the process was identified among several viruses such as HIV, RSV, rhinovirus, dengue virus, human parainfluenza virus. Additionally, hamper the receptors which transmit the signal to provoke the production of type I IFN through the creation of hydrogen peroxide inside the endosome of phagocytic cells which creates the oxidation of Cys98 on TLR7 (To et al., 2017).

The human TLR is capable to identify viruses inside the endosome, triggering transcription factors (NF-kB, IRF3, and IRF7), and inductions of interferon synthesis through the TIR domain. TIR complex including TLR-MyD88 protein, recruits, and induction interleukin-1R-associated kinase (IRAK) by phosphorylation. IRAK corresponded to TNF receptor-associated factor 6 (TRAF6) and induced an array of pathways that eventually turns to alteration of IFN gene expression (Xagorari and Chlichlia, 2008, Kiziltaş, 2016, Barton and Medzhitov, 2003) (Figure 2). SARS-CoV blocks the signaling of RNA sensors, and inhibits IRF3 gene transcription, either directly or indirectly, during ubiquitination and degeneration of RNA sensing adaptor molecules MAVS and TRAF3/6 (Kindler et al., 2016). Animal models reveal that impairment in TLR3 or TLR4 was fatal to SARS-CoV infection (Totura et al., 2015). Consequently, TLR partners with sensitivity to infectious disease, a mutation in single amino acid, eventually affect the immune response mechanism (Wang et al., 2014, Totura et al., 2015).

2.1.2. (RIG-I)-LIKE RECEPTORS

Retinoic acid-inducible gene I (RIG-I)-like receptors are a member of family DExD/H box RNA helicases, play a crucial role in viral RNA sensing infection and activate and modulate innate immune responses against the virus. RIG-I identifies RNA-virus stimulates the downstream signaling series, then induces a stress response, promoting RLP-mediated viral defense (Yoneyama et al., 2015). Three types of RPL have been described in humans and mice, which consist of members RIG-I, melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), within the endosome dsRNA sensed by TLR3, while in the cytosol by RIG-I and MDA5 (Yoneyama et al., 2016).

RPLs protein wildly displayed on most cells that function as downstream signal activation of transcriptional factor to run ISGs finally cause type IFN-1production, the expression of RPLs generally in resting cells at low levels, seems to be dramatically increased when encountering IFN and virus infection (Loo and Gale Jr, 2011, Kang et al., 2004, Yoneyama et al., 2005).

Despite stimulating IFN gene expression and production against viral infection, RPLs can also enhance the IFN-λ family of IL-10 cytokine expression collectively known as type III interferon and other pro-inflammatory cytokines, a significant role in controlling infections (Donnelly and Kotenko, 2010, Poeck et al., 2010).

Viral RNA of CoV expresses proteins in the cytoplasm, recognized by RPL, and stimulates mitochondrial antiviral signaling which occurs in the cytokine synthesis, including IFNs to confine viral replication (Yoneyama et al., 2015). RIG-I has a DExD/H box RNA helicase structure and a C-terminal termination structure (CTD) and works together with MDA5, an N-terminal caspase recruitment structure (CARD) that impedes with MAVS downstream cascade. Viral RNA demonstrated by the C-terminal RNA helicase with CTD leads to configurational modifications that consume ATP to the formation of CARD interaction with MAVS, ultimately affecting the tumor necrosis factor receptor-associated factor 3 (TRAF3). TRAF2/6 is further activated NF-κB through recruited MAVS. Results in the stimulation of IRF3 and binds to NF-κB IFN-β promoter and express IFN-β gene (Yoneyama et al., 2015, Loo and Gale Jr, 2011, Ford et al., 2010).

2.1.2. TYPE I INTERFERONS

Interferons (IFNs) are pro-inflammatory cytokines, functions required in body defense against microbial infections (Kovarik et al., 2008). Type I IFN has anti-proliferative and antiviral activity through IFN receptors of cells, particularly plasmacytoid dendritic cells, followed by recognition of viral particles PRR. IFN α/β is activated by binding to the type I IFN alpha receptor (IFNAR), ultimately activating the signal transcription of interferon genes through the JAK/STAT pathway (Levy and Darnell, 2002).

Attachment of type I INF (IFNα and IFNβ) onto the cognate receptor leads to activation JAK-STAT pathway so that Janus kinases JAK1/TYK2 to be turned on inside of cytosol by mediated of IFAR1 and IFAR2 on the surface of cells, followed by STAT and STAT2 phosphorylate finally create a complex with IRF9, after entering the nucleus induce the expression of antiviral gene programs (ISGs) (Bekisz et al., 2004), this signaling pathway is represented in (Figure 2).

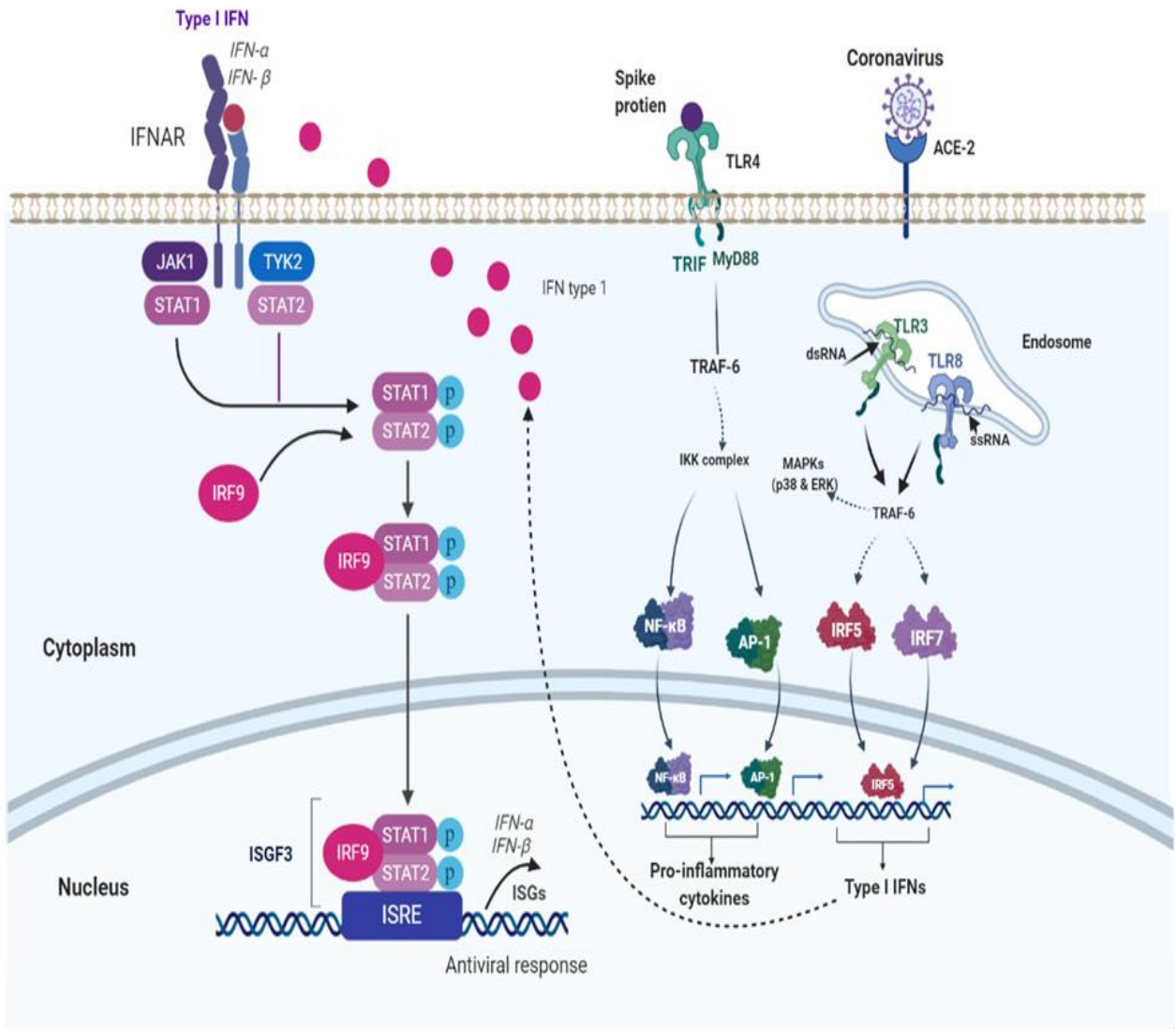

Figure 2. Mechanism of innate immune response mediates by Toll-like receptors and IFN type I against CoV (app.biorender.com)

Moreover, Muller et al. (1994) exhibited that mice IFNAR lacking are more vulnerable to viral infections , such as vesicular stomatitis virus (VSV). Besides, another investigation reported that when HBV infection, IFN-γ, and IL-2 are elevated significantly in the patient's serum decided that IFN-γ is required for host antiviral immunity against HBV infection, while IL-4 and IL-10 which are secreted by T helper-2 cells are associated in the humoral immunity (Ahmed and Al-Barzinji, 2009, Ahmed and Al-Barzinji, 2011). ORF 6 protein of SARS-CoV suppresses IFN type 1 production via inhibition of IFN-induced JAK-STAT signaling and preventing the nuclear translocation of phosphorylated STAT1 and consequently hide from innate immunity response (Perlman and Netland, 2009, Kopecky-Bromberg et al., 2007, Frieman et al., 2007). Please arrange the references according to the achievement years from older to newer ones.

In a word done in 2006, it was reported that MERS-CoV M protein and other non-structural proteins, such as ORF 4a, ORF 4b, and ORF 5, mediates IFN-β antagonism by the interference of interferon promoter and IRF-3 actions (García-Sastre and Biron, 2006). Furthermore, it is determined in a bat that SARS-like coronavirus (SL-CoV) inhibits IFN production via IRF3b homologous with the same IFN antagonism action as those realized in the human immune system (Zhou et al., 2012).

In vitro studies revealed that administration of IFN α or IFN β could suppress SARS-CoV replication, although it diminishes the severity of

SARS-CoV infection (Zheng et al., 2004, Spiegel et al., 2004, Cinatl et al., 2003). Another investigation in an animal model of SARS-CoV or MERS-CoV infection mentioned that hyper-production of IFNs and monocyte-macrophage inflammatory cells increase innate immunity and results in pneumonia (Zumla et al., 2015, Prompetchara et al., 2020). Consequently, SARS-CoV-2 shares more likely to SARS-CoV in its structure and genomic composition; therefore, we suppose interferon type 1 might have the same block action as SARS-CoV-2 replications and reduce viral severity on the infected patients by stimulating an antiviral immune response.

2.1.3. DENDRITIC CELLS (DCS)

Dendritic cells (DC) are professional antigen-presenting cells (APCs) that play a crucial role in host immunity by combining innate to adaptive immune responses (Galati et al., 2022). They can recognize emergency signal infected pathogens, followed by the activation of naive T lymphocytes, and trigger an immune response against infectious microbes. These cells via the TLR or other PRRs can recognize pathogenic particles (Guermonprez et al., 2002, Lemaitre et al., 1996).

Induction of myeloid DC with a TLR3 ligand poly (I: C), a synthetic analog of double-stranded viral RNA, is associated with the discharge of pro-inflammatory cytokines by mDC1, but not by mDC2. These assumed another role for mDC1 in the recognition of viruses in the respiratory tract by innate immunity (Akesolo et al., 2022).

It acts as antigen-presenting cells via MHC molecules to lymphocytes, and can identify antigens through TLR, such as bacterial DNA, dsRNA of a virus, and LPS (Xagorari and Chlichlia, 2008). After exposure to a foreign agent, they migrate to the T riches area of the lymph nodes and undergo maturation. It is mediated by T-cell stimulation that results in the upregulation of cell surface costimulatory molecules and MHC class I and II (Banchereau et al., 2000, Ali et al., 2022a). In a study done in 2007, the role of plasmacytoid dendritic cells (pDCs) and pDC-derived IFNs class I on the immunopathogeneses of mouse hepatitis virus infection (MHV)was seen, in which pCD inhibits the replication of CoV that is mediated by production of type IFNs, pCD can detect MHV through TLR7 after exposure to RNA virusCervantes-Barragan et al. (2007).

ACE-2 receptor is not expressed on DC; for this reason, endocytosis is mediated by macropinocytosis (Law et al., 2005), this could be done with the assistance of C-type lectins, such as CD209 (DC-SIGN), CD209L (L-SIGN), or CD206 (mannose receptor), and mannose involved in the spike structure of the CoV. Consequently, C-type (CD209L) protein may be associated with the other form of SARS-CoV entering the cells (Marzi et al., 2004, Jeffers et al., 2004).

Yang with co-workers in 2004, illustrated that DC could engulf SARS-CoV, then transfer it to susceptible cells in the lung that have a vital role in developing SARS-CoV disease in the host. It is also concluded that DCs serve as a reservoir of viruses and share with chronic infection. In consequence, it may influence antigen presentation and eventually influence SARS-CoV antibody-mediated immunity (Yang et al., 2004).

The report conducted by Tseng et al. (2005) demonstrated that DC aborts to initiate vigorous IFN response but leads to the up-regulation of pro-inflammatory cytokines and chemokines. MERS-CoV could infect a wide range of immune cells, including monocyte and T cells, that it also could be infected DC. The efficiency of MERS-CoV in DC infection might refer to the numerous DPP4 cellular receptors found on activated white blood cells (Raj et al., 2013).

3. EVADE OF CORONAVIRUS FROM INNATE IMMUNE RESPONSES

The receptors of innate immunity can discriminate between self and non-self-antigens, involve in viral particle recognition, and restrict viral replications through antiviral protein expressions (Prompetchara et al., 2020). Several cytoplasmic viruses including CoVs, evade from the innate body defenses by hiding their viral components and delimitating encounters with sensors or by blocking the effects of interferons mediated by the expression of viral antagonists (Kindler et al., 2016).

CoVs can practice different strategies to elude innate immune responses (Figure 3), particularly type I IFN responses, and intensify disease severity (Channappanavar et al., 2016). The studies conducted by a group of researchers in

2007 described that ORF3a and ORF6 proteins interfere with type I IFN generation by diminishing the IFNAR levels via proteolytic degeneration and ubiquitination and prevent STAT1 nuclear import sequentially (Kopecky-Bromberg et al. (2007). In MERS-CoV, ORF4a is the protein that suppresses IFN induction by interacting with the viral genome and the cofactors Protein Activator (PACT) RLR (Totura et al., 2015). Additionally, CoVs ORF3b antagonizes to IFN type I signaling cascade and eventually interferes and inhibits the pathway of effector cell activation that requires destruction and aborts viral replication (Freundt et al., 2009). Furthermore, SARS-CoV papain-like protease (PLP) can obstruct IFN signaling by a deteriorating pathway of IRF3 and NF-κB phosphorylation and nuclear translocation by the system (Sun et al., 2012).

Coronavirus nonstructural proteins are needed for replication of the virus in addition to neutralizing innate immune responses. The nsp1 proteins of SARS-CoV capable of impeding and cooperating with translational machinery bioactivity of the host through binding to the small ribosome subunit, suggesting that CoV nsp1 play a critical role in the viral pathogenicity (Zust et al., 2007, Kamitani et al., 2009). CoV nsp15, which EndoU designates, has endoribonuclease activity and antagonist to IFN, which mimic XendoU cellular endoribonuclease, suggested that EndoU was vital viral RNA replication in cell culture (Deng et al., 2019, Ivanov et al., 2004); the investigations was explained that the action of EndoU is necessary to reduce viral RNA sensing by MDA5 (Kindler et al., 2017). A study done in 2020 by Hackbart et al. (2020) explained that the activity of CoV EndoU reduces the intensification of the polyuridine (PolyU) on 5′-PolyU negative-sense RNAs, assuming that the machinery of EndoU able to break PolyU and cooperate with MDA5 activity finally repress initiate of antiviral innate immune responses (Hackbart et al. (2020).

Dodging of SARS-CoV from innate immune responses needs avoidance of viral PAMPS recognized by cellular PRRs. During viral replications, dsRNA intermediates partitions accumulated inside of vesicles may be masking and cover the viral components from exposure by cytosolic PRRs (Snijder et al., 2006, Knoops et al., 2008). One-point variations between eukaryotic mRNAs from viral mRNAs lack a 5′cap in mRNAs of viruses, although unusual viruses similar to the host can cap mRNA structure. SARS-CoV nsp14 guanine-N7-methyltransferase action is the first step to building an RNA cap that structurally mimics to host RNA cap; consequently, discrimination of viral mRNAs from host mRNAs is more difficult by the innate host immunity (Lou and Rao, 2022, Ali et al., 2022b).

Understanding the mechanisms of CoV evasion from innate immunity support to design and development of new targets of antiviral drugs, other than non-structural proteins, structural proteins of CoVs have been identified as impeding IFN signaling and production (Zhang et al., 2022).

SARS-CoV N protein seems to be hampered by IFN synthesis, supposed that N protein interacts with RNA identification immune sensors for an instant; MAD5 and RIG-I eventually act as an inhibitor in IFN production. Additionally, the M protein of CoVs interacts with IFN type I production effect like N protein has been shown to inhibit IFN signaling. SARS-CoV M protein showed associated down-regulate IFN production by blocking TRAF3·TANK·TBK1/IKKε complex formation, although IFN production blocked by MERS-CoV M protein suggested that M protein blocking IRF3 translocation into the nucleus (Lu et al., 2011, Siu et al., 2009, Yang et al., 2013). CoV obstructs several steps during an initial non-specific immune response, including RNA sensing (1,2), signaling pathways of type 1 IFN synthesize (3), STAT 1/2 trigger downstream activation of IFN/IFNAR (4) (Kumar et al., 2020).

4. CONCLUSION

The breakout of SARS-CoV-2 leads to a global public health crisis. Coronaviruses infect epithelial cells in the lungs and deteriorate tissues by attracting inflammatory cells by pro-inflammatory cytokines and causing pneumonia. The receptors of innate immune systems can recognize viruses through PAMPs and reduce viral spread through antiviral responses mediated by TLR and type I IFNs Although DCs are powerful antigen-presenting cell that resides in most tissues, and determines coronavirus particles with the aid of CD209L and finally for virus clearance from host tissues.

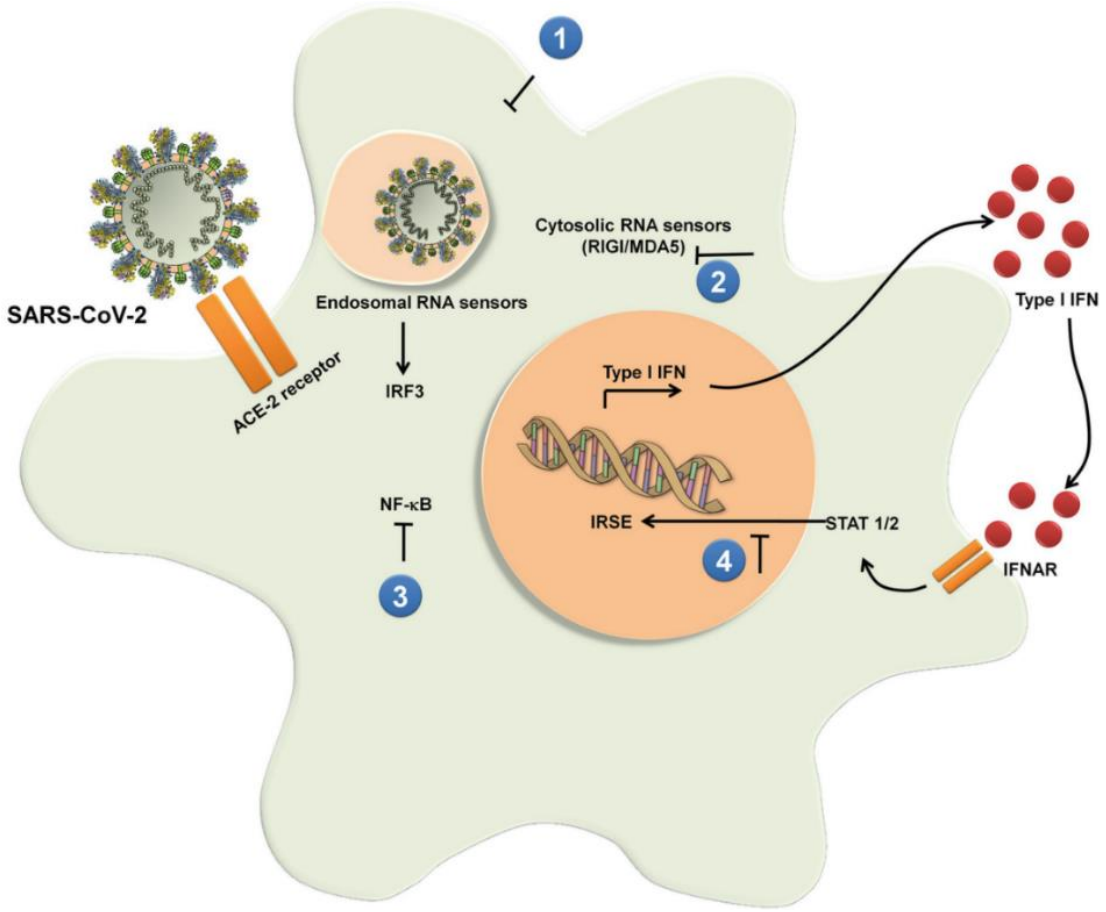

Figure 3. Mechanism of SARS-CoV escaping from innate immune responses by SARS-CoV. CoV obstructs several steps during the initial non-specific immune response including RNA sensing (1, 2), signaling pathways of type 1 IFN synthesize (3), STAT 1/2 trigger downstream activation of IFN/IFNAR (4) (Kumar et al., 2020).

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Coronaviruses can evade themselves from innate body defenses by hiding their viral components and delimitating encounters with sensors or by inhibiting the effects of IFN mediated by the expression of viral antagonists. The studies revealed that type IIFNs effectively suppress viral replications; therefore, we assumed that administration of IFN type I might aid in the patient's healing and elimination of the virus. Besides, we demonstrate the known scope of activities of humans, special immune cells in innate immunity, and may probably combine with viruses including SARS-CoV-2. Additionally, we give an outline of COVID-19 in which they may be involved in the context of immunity.

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Conflict of Interest

No author reports any conflicts of interest that are related to this article.

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