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Role of toll-like receptor 7/8 pathways in regulation of interferon response and inflammatory mediators during SARS-CoV2 infection and potential therapeutic options

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) is the causative agent of Corona Virus Disease 2019 (COVID-19). Lower production of type I and III interferons and higher levels of inflammatory mediators upon SARS-CoV2 infection contribute to COVID-19 pathogenesis. Optimal interferon production and controlled inflammation are essential to limit COVID-19 pathogenesis. However, the aggravated inflammatory response observed in COVID-19 patients causes severe damage to the host and frequently advances to acute respiratory distress syndrome (ARDS). Toll-like receptor 7 and 8 (TLR7/8) signaling pathways play a central role in regulating induction of interferons (IFNs) and inflammatory mediators in dendritic cells. Controlled inflammation is possible through regulation of TLR mediated response without influencing interferon production to reduce COVID-19 pathogenesis. This review focuses on inflammatory mediators that contribute to pathogenic effects and the role of TLR pathways in the induction of interferon and inflammatory mediators and their contribution to COVID-19 pathogenesis. We conclude that potential TLR7/8 agonists inducing antiviral interferon response and controlling inflammation are important therapeutic options to effectively eliminate SARS-CoV2 induced pathogenesis. Ongoing and future studies may provide additional evidence on their safety and efficacy to treat COVID-19 pathogenesis.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) is a positive-sense single-stranded RNA virus (29.9 kb) that belongs to the class IV group of viruses according to the Baltimore classification and causes Corona Virus Disease 2019 (COVID-19). This disease emerged as

Abbreviations: TLR, toll like receptor; MYD88, Myeloid Differentiation primary response protein 88; CD14, cluster of differentiation 14; LBP, lipopolysaccharide binding protein; MD-2, myeloid differentiation protein 2; ST-2, growth stimulation expressed gene 2 or interleukin 1 receptor like 1 (IL1RL1); TIRAP, 'TIR' domain containing adaptor protein; IRAK, interleukin 1 receptor associated kinase 1; TOLLIP, toll interacting protein; PKR, protein kinase R; TRAF, TNF receptor associated factor; TAB, TGFβ activated kinase (MAP3K7) binding protein; TAK1, TGFβ activated kinase 1; SITPEC or ECSIT, ECSIT signaling integrator; MKK, mitogen activated protein kinase; NIK, NF-kappa-beta inducing kinase; MEKK1, MAPK/ERK kinase kinase 1; IKK, inhibitor of nuclear factor kappa B kinase; IκBα, I kappaB alpha; NFκB, nuclear factor kappaB; PPAR, peroxisome proliferator activated receptor alpha; JNK1, JUN N-terminal kinase; ELK-1, ETS like gene 1 tyrosine kinase oncogene; JUN, jun oncogene; IL-1, interleukin 1; TNFα, tumor necrosis factor alpha; IL-12, interleukin 12.

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a major pandemic globally and is a severe threat to the world's economy with increasing new infections daily. As of June 10, 2020, over 175.7 million people have been infected, and over 3.79 million people have died of COVID-19. According to the WHO, following the identification of SARS-CoV2 in Wuhan, China, the virus rapidly spread to all countries in the world in less than four-months [1]. However, two of the spike protein RNA carrying lipid based or adenovirus based spike protein DNA carrying vaccines are proved to be effective in protecting humans from SARS-CoV2 infections and variants and approved by FDA [2–5].

In humans, the spike protein of SARS-CoV2 interacts with angiotensin-converting enzyme 2 (ACE2) receptors expressed on the surface of epithelial cells present in the lung, gut, and other organs, thereby establishing infection [6]. COVID-19 is symptomatically characterized by high fever, cough, general malaise, and a pathology associated with immediate and robust production of pro-inflammatory cytokine mediators in blood, lung, gut, and other tissue compartments [7,8]. Symptomatic patients may advance to acute respiratory distress syndrome (ARDS) displaying pneumonitis, shock, organ failure, and even death [8–11]. Currently, a comprehensive understanding on the role of inflammatory mediators released into the plasma and expressed in peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage fluid (BALF) is unavailable. Potential therapies to induce vital type I interferon (IFN) responses and control inflammation and their association with the regulation of TLR pathways are still under investigation. This review focuses on i) inflammatory mediators observed in plasma, PBMCs and BALF samples of SARS-CoV2 infected preclinical models and patients; ii) regulation of type I IFNs during coronaviral infections; iii) current and potential therapies to limit SARS-CoV2 replication and pathogenesis; iv) toll-like receptor (TLR) mediated antiviral and inflammatory responses during coronaviral infection and v) TLR7/8 agonists as potential therapeutics to treat coronaviral infections.

2. Role of pro- and anti-inflammatory cytokines and other mediators in COVID-19 pathogenesis

Inflammation is the primary response initiated by immune cells in the body of pathogen infected individuals to limit replication of the pathogen in target cells and prevent tissue damage. Robust and high level of cytokine and chemokine production following infection, which termed as cytokine storm and may cause severe tissue damage and was observed in SARS, MERS and SARS-CoV2 infections [12–14]. Cytokine storm contributes to progressive lung tissue damage and the development of often fatal ARDS [15]. Over 30 different cytokine levels are altered following SARS-CoV2 infection in the plasma of COVID-19 patients [7,14,16]. Several of the pro- and anti-inflammatory cytokines are known to increase plasma SARS-CoV2 RNA copies, disease severity and ARDS (Table 1). Preclinical and clinical studies have provided several lines of evidence on pro- and anti-inflammatory cytokines released into peripheral blood of corona virus infected animal models and patients [7,14,16]. A study conducted by Blanco-Melo et al. showed that normal human bronchial epithelial cells (NHBE) infected with SARS-CoV2 at 2 multiplicity of infection (MOI) produced C-C motif chemokine ligand (CCL) 20, C-X-C motif chemokine ligand (CXCL) 1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL16, interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNFα) in the blood as early as 24h post infection [22]. In the same study, a SARS-CoV2 infected ferret model displayed increased expression of CCL2, CCL8, and CXCL9 transcripts in upper respiratory tract tissue [22]. Later, Huang et al. analyzed 27 cytokine profiles in the plasma of 41 COVID-19 patients during the acute phase of infection using the Bio-Plex 200 system [7]. This study reported an increase in levels of IL-1β, interleukin 1 receptor antagonist (IL1-RA), IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF as compared with healthy volunteers [7]. In the same study, comparison between patients admitted to ICU showed higher IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNFα levels as compared with non-ICU patients. Further, cytokine and chemokine analyses in sera of 24 SARS-CoV2 RNA positive individuals (n = 24), portrayed elevated levels of CCL2, CCL8, CXCL2, CXCL8, CXCL9, CXCL16, IL-6 and IL-1RA as compared with healthy controls (n = 24) [7]. In general, chemokines attract immune cells to the site of localization, which initiate inflammatory response to limit viral infection. Infiltration of leukocytes expressing CD163 (monocytes and macrophages), CD226 (NK cells, platelets, monocytes and a subset of T cells), CCR5 (T, NK cells, monocytes and macrophages), CCR6 (dendritic cells (DCs) and memory T cells), CXCR1/CXCR2 (promononuclear cells (PMNs), neutrophils, basophils and eosinophils, monocytes and endothelial cells), and CXCR7 surface receptors contribute to heightened pro-inflammatory responses [22]. Consistent with existing evidence, recent reports have indicated that enhancement of CXCL9 and CXCL16 [23] attracts T and natural killer (NK) cells. Further, CCL2 and CCL8 [23–25] expression attracts monocytes and macrophages. In addition, CXCL8 expression attracts neutrophils [18,23,26] in large numbers to

Table 1
Pro- and anti-inflammatory cytokines, chemokines and other mediators influencing SARS-CoV2 replication and ARDS.

S. No	Factors	Description	Influence	Level	References
Pro-inflammatory mediators					
1	IFNγ	Interferon gamma	ARDS	Low	[19]
2	IL-1α	Interleukin 1 alpha	ARDS	High	[16]
3	IL-1β	Interleukin 1 beta	ARDS	High	[18]
4	IL-2	Interleukin 2	ARDS	High	[7,16]
5	IL-4	Interleukin 4	ARDS	High	[16]
6	IL-6	Interleukin 6	ARDS	High	[18–21]
7	IL-7	Interleukin 7	ARDS	High	[7,16]
8	IL-8	Interleukin 8	ARDS	High	[18]
9	IL-12	Interleukin 12	ARDS	High	[16]
10	IL-17	Interleukin 17	ARDS	High	[16]
11	TNFα	Tumor necrosis factor alpha	ARDS	High	[7,18–20]
12	CCL2/MCP-1	C-C motif Chemokine Ligand 2	ARDS	High	[7]
13	CCL3/MIP-1α	C-C motif Chemokine Ligand 3	ARDS	High	[7]
14	CCL7/MCP-3	C-C motif Chemokine Ligand 7	High viral load, ARDS	High	[14,17,20]
15	CXCL-9/MIG	C-X-C motif Chemokine Ligand 9	ARDS	High	[14]
16	CXCL10/IP-10	C-X-C motif Chemokine Ligand 10	High viral load, ARDS	High	[7,14,16,17]
17	CSF1/M-CSF	Colony Stimulating Factor	ARDS	High	[16]
18	CSF2/GM-CSF	Colony Stimulating Factor 2	ARDS	High	[7]
19	CSF3/G-CSF	Colony Stimulating Factor 3	ARDS	High	[7,16]
20	IL-2R (Soluble)	Interleukin 2 receptor	ARDS	High	[19]
21	S100-A12/EN-RAGE	Protein S100-A12	ARDS	High	[20]
22	HGF	Hepatocyte growth factor	ARDS	High	[14]
23	OSM	Oncostatin M	ARDS	High	[20]
Anti-inflammatory mediators					
1	IFNα	Interferon alpha	ARDS	Low	[20]
2	IFNα2	Interferon alpha 2	Lung injury, ARDS	High	[16]
3	IL-1RA	Interleukin 1 receptor antagonist	High viral load, ARDS	High	[14,16,17]
4	IL-10	Interleukin 10	ARDS	High	[7,19]

BALF. Migration of these cells to lung tissue may potentially can drive profound inflammation and advances lung pathology [22]. In severe COVID-19 cases, CD4, CD8, NK and plasmacytoid DCs were reduced, while activated (HLA-DR+ CD38 +ve) CD4, CD8, NK cell numbers were increased in blood demonstrating hyper immune activation [27–29]. Large numbers of pro- and a few anti- inflammatory cytokines, chemokines and other mediators are increased in the plasma of SARS-CoV2 infected persons and may enhance viral replication, disease severity and may cause ARDS (Table 1). Pro-inflammatory microenvironment maintained by heightened pro-inflammatory factors, extremely low levels of anti-inflammatory factors contribute to hyperimmune activation thereby may cause lung injury in severe SARS-CoV2 infected persons [30]. This hypothesis was further supported with the evidence obtained on increased bacterial products (lipopolysaccharides) observed in the plasma of severe SARS-CoV2 infected persons who have advanced to ARDS [20]. Hyperimmune activation in COVID-19 patients was correlated with increased plasma IL-6, TNFα, MCP-3, EN-RAGE, TNFSF14, and OSM levels [20]. Higher numbers of HLADR+ CD38+ CD4, CD8 and NK cells and increased quantity of microbial products in blood were also observed in HIV infected patients which contribute to hyperimmune activation [31–33]. Similar findings were observed in HIV infected persons who have showed higher non-specific activation of CD4 and CD8 T cells and translocation of microbes from the gut to peripheral blood compartments, which advance the disease to AIDS [31–33]. Previous reports showed that reduced hyperimmune activation could control HIV infection and improves T cell function [33,34]. Though these pathogenic mechanisms were similar between HIV and COVID-19, an interesting difference was noticed on regulation of type I interferon response. Sustained high levels of IFNα was observed in all stages of progressive HIV infection and is a major contributor of hyperimmune activation [31–33,35], in contrast, higher initial but lower IFNα levels were observed in plasma of COVID-19 patients during the progressive infection and disease severety [20,36,37]. Future studies should focus on investigating the reasons for microbial translocation and associated non-specific activation of immune cells that are observed during maintenance of low levels of type I interferons in COVID-19 patients.

In addition to the evidence on inflammatory mediators increased in plasma and serum collected from SARS-CoV2 infected patients, PBMCs collected from COVID-19 patients with varying clinical severity (n = 8) were used to characterize immunophenotypes and inflammatory mediators using single cell RNA sequencing approach [38]. In this, CCL3, CXCL10, IFNγ, IL-1β, TGFβ1, and TNFα transcripts were increased in PBMCs with a specific association of TNFα and IL-1β cytokines with monocytes and DCs as compared with healthy controls (n = 4) [38]. IFNγ and CXCR3 induction have also predicted a Th1 bias in immune response during SARS-CoV2 infection, which may lead to the production of several cytokines and chemokines that cause aggravated inflammatory response. Further understanding of transcription factors controlling inflammatory response is evident by increased activation of nuclear factor kappa-light-chain-enhancer-of activated B cells 1 (NFκB1), NFκB2, signal transducer and activator of transcription 1 (STAT1) and IFN regulatory factor-1 (IRF1) in this cell analyses [38]. SARS-CoV2 RNA and TLR7/8 interaction driven production of interferons (IFNs) and inflammatory mediators and their further contribution to COVID-19 pathogenesis is summarized in Fig. 1.

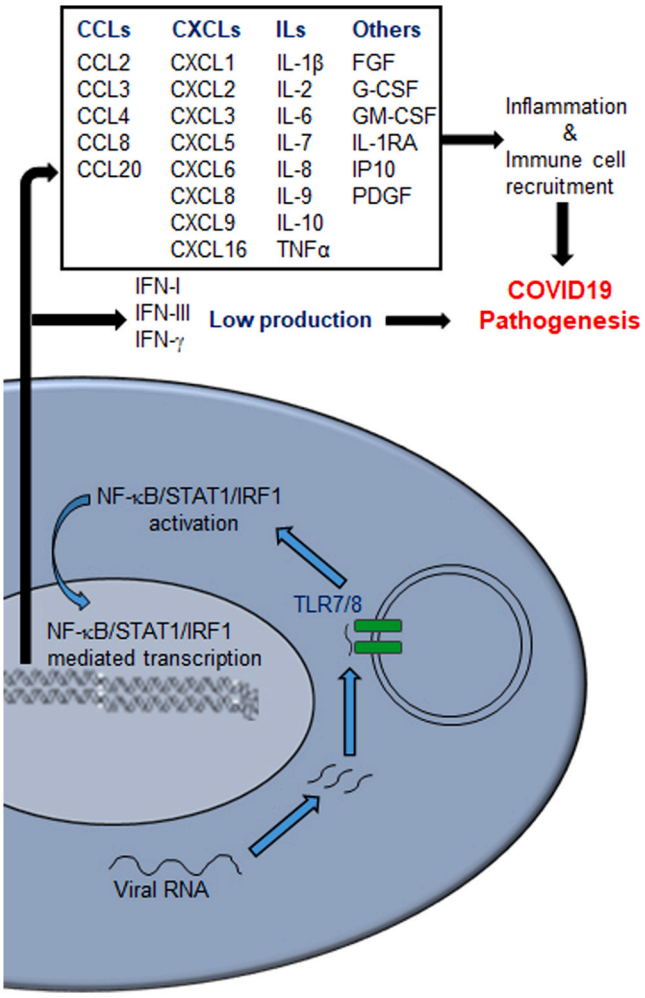

Fig. 1. SARS-CoV-2 RNA interacts with toll like receptor 7 and 8 receptors present on endosomes and thereby induces high levels of IL-1β, IL-2/6/7/8/9/10 cytokines, CCL2/3/4/8/20, CXCL1/2/3/5/6/8/9/16 chemokines and other inflammatory mediators such as fibroblast growth factors (FGFs), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 1 receptor antagonist (IL-1RA), interferon induced cytokine 10 (IP-10) and platelet derived growth factors (PDGFs) but may induce low level of type I, III and gamma (γ) interferons which contributes to COVID-19 pathogenesis.

3. Reduced type I IFN responses and mechanisms to escape antiviral responses during corona viral infections

Type I IFN (IFNα/β) induction is a central event in innate immune responses initiated as a part of the defense against SARS-CoV2 infection. Type I IFNs are produced by pDCs, monocytes and macrophages [37,38]. Type I IFNs enhance DC maturation, regulate T cell growth properties and promote NK and CD8 T cell-induced cytotoxicity [39]. In contrast to initial reports, increasing evidence suggests that patients with severe COVID-19 have a delayed and blunted type I IFN response [40,41]. In SARS-CoV2 infected preclinical NHBE and ferret models and clinically symptomatic persons, low plasma IFN-I/-III levels have been observed. This finding is significant as the lack of host associated immune defenses have been shown to increase disease severity [22,27]. In contrast, Zhou et al. showed higher amounts of interferon stimulatory genes (ISGs) in BALF [41]. Though additional evidence is needed, the existing results have demonstrated that compartmentalized type I IFN responses are observed in COVID-19 patients. This observation can be further explained by the increased number of type I IFN producing pDCs, which may have migrated from peripheral blood to lung and gut tissue due to induction of migratory molecules such as α4β7 [31,42–44]. T cells and pDCs migrate to gut tissues with their ability to bind α4β7 with MadCAM1 receptor and may cause inflammation [31,42–44]. Aggravated inflammation due to increased production of cytokines, chemokine mediators and hyper activity of immune cells including pDCs in lung tissue may cause ARDS, and sustained inflammation may lead to multiple organ failure and ultimately death in COVID-19 patients [45]. Strategies to control inflammation may reduce disease severity and thereby increase the survival rate of COVID-19 patients.

Coronaviruses have developed unique immune evasion strategies to escape host-mediated antiviral innate immune response [46] thereby preventing type I IFN induction [47]. SARS-CoV associated non-structural proteins 1 (nsp1), nsp3, N proteins were known to prevent type I IFN responses [48]. In addition, SARS-CoV associated papain-like protease (PLPro) inhibits TLR7 induced type I IFN production through suppression of IRF-3, Nuclear Factor-κB (NF-κB) and Activator Protein-1 (AP-1) in human promonocytes [49]. Exposure of viral RNA activates RIG-I/MDA5 mediated signaling cascade that promotes activation of downstream adaptor proteins MAVS/TRAF3/-TRAF6/TOM70, which may ultimately regulate production of IFNβ and thereby induce an antiviral state in infected cells [50]. SARS-CoV2 Orf9b suppresses type I IFN response through association with TOM70 [50]. The high rate of RNA viral replication, resulting in the generation of large amount of viral genomic RNA transcripts that induce robust TLR mediated inflammatory cytokine production, may exert detrimental effects on the immune system and tissue microenvironment [51,52]. Currently, information on comparative analysis of SARS, MERS and SARS-CoV2 genomic RNA induced TLR mediated inflammatory processes is unavailable in systemic and tissue compartments. Further evidence on pathogenic effects observed during SARS-CoV2 TLR mediated pathways involvement will help in development of novel therapeutic strategies to reduce immunopathogenesis.

4. Current and potential therapies to limit SARS-CoV2 infection and COVID-19 pathogenesis

Currently, therapeutic options to treat COVID-19 patients are limited. Remdesivir is a chemotherapeutic small molecule inhibitor of RNA-dependent RNA polymerase (RDRP) activity of SARS-CoV2 approved to treat COVID-19 patients in the United States. SARS-CoV2 infected patients who received remdesivir therapy achieved clinical endpoint recovery (e.g., hospital discharge) at a faster rate as compared to placebo controls [53,54]. Following administration of remdesivir, penetration into human cells generates the antivirally active GS-441524 monophosphate metabolite analogous to adenosine nucleoside triphosphate. This metabolite shows antiviral activity through inhibition of RDRP activity and thereby limits viral replication [54]. In critically ill COVID-19 patients admitted to the ICU, more than 44% mortality rate was observed even after receiving remdesivir therapy [54]. In this study, 35 patients were enrolled, including 18 in ICU and 17 in infectious disease ward (IDW). A ten day remdesivir course was completed by 22 (63%) of these patients [54]. On day 28, 14 (82.3%) of 17 patients in IDW were discharged, two were still receiving care in the hospital and one (5.9%) died. In ICU, 6 (33.3%) were discharged following their recovery, three (16.7%) were mechanically ventilated and one (5.6%) was improved but still hospitalized. Whereas, 8 patients (44%) died [54]. Hypertransaminasemia (42.8%) and acute kidney injury (22.8%) were the most frequent severe adverse events in these patients [54]. Later, in a phase 3 randomized, double-blind, placebo-controlled trial (NCT04257656), remdesivir efficacy was evaluated in 158 patients with standard dose (200 mg on day 1 and 100 mg on day 2 through 10 days) as compared with placebo (n = 79) controls [55]. There were no significant differences in mortality and time to clear the virus from COVID-19 patients between the two groups [55]. Further studies are necessary to provide additional evidence on the efficacy of remdesivir to treat severe SARS-CoV2 infection [54]. In addition to remdesivir, several antiviral and anticancer drugs were repurposed to evaluate their effectiveness against SARS-CoV2 infection [56]. Reducing inflammation is important to increase the rate of recovery of severely SARS-CoV2 infected patients and to reduce ARDS. Corticosteroids promote vasoconstriction and may decrease migration of leukocytes to sites of inflammation. Dexamethasone, an immunomodulatory synthetic adrenal corticosteroid has shown to have anti-inflammatory properties. Recently, the results from RECOVERY trial showed that among eight of the mechanically ventilated COVID-19 patients, the use of dexamethasone prevented death of one person showing preliminary evidence to reduce mortality [57]. In another study, of 21 COVID-19 patients treated with dexamethasone, 71% of the patients showed reduced plasma C-Reactive Protein (CRP) levels from initial 129.52–40.573 μg/mL indicating the decrease in disease severety. In this study, patients were discharged home with a mean length of stay of 7.8 days [57]. However, dexamethasone showed no benefit to patients with mild disease (i.e., patients who did not require any oxygen) [57]. Since dexamethasone suppresses the immune system, initially, patients with severely inflamed lung tissue may experience some relief. However, a functional host immune system is vital to combat SARS-CoV2 infection and thereby the use of dexamethasone in these patients with various stages of the disease is mechanistically debatable.

Recombinant interferons were used as therapeutic agents to treat viral infections including SARS-CoV and SARS-CoV2. Type I/III interferons were therapeutically and prophylactically utilized to treat COVID-19. As of April 3, 2021, there were 30 studies of type I/III IFNs were registered on clinicaltrials.gov (ClinicalTrials.gov) and six studies (NCT04343768; NCT04350281, NCT04349410, NCT04276688, NCT04492475 and NCT04276688) were completed. In these studies, IFNα-1A/1B and IFNα-2B were used to treat COVID-19 patients in combination with hydroxychloroquine alone (NCT04350281) or with hydroxychloroquine + lopinavir/ritonavir (NCT04343768) or lopinavir/ritonavir + ribavirin (NCT04276688) or with multiple combinations (NCT04349410). In another two clinical trials, IFN-β-1a/1b was used along with remdesivir (NCT04492475) or lopinavir/ritonavir or ribavirin (NCT04276688). In COVID-19 patients, treatment with IFNα not only reduced virus replication but also accelerated recovery from lung tissue dysfuncyion [58]. Published data on the therapeutic and prophylactic use of interferons in the treatment of COVID-19 are limited. In 77 COVID-19 patients, IFNα-2b plus arbidol (an anti-influenza drug) treatment reduced viral RNA copies in the upper respiratory tract and reduced IL-6 and CRP biomarkers, indicating the decrease in disease severety [41]. In another study, IFNβ-1a treatment in 44 COVID-19 patients along with hydroxychloroquine plus lopinavir/ritonavir or atazanavir/ritonavir showed some benefit with a 23.1% increase in hospital discharge rate and 24.6% reduction in mortality rate as compared with patients on standard drug regimen [59]. Collectively data generated from these studies have demonstrated the use of IFNs as a promising therapeutic approach to treat COVID-19 patients. In a group of low-risk (n=2415) healthy persons, administration of 2–3 nasal drops of recombinant human IFNα (rhIFNα) for four times a day, and in a group of high-risk (n=529) healthy persons, administration of hrIFNα combined with thymosin-α1 (1.6 mg, hypodermic injection, once a week) for 28 days protected from SARS-CoV2 infection [60]. These studies have demonstrated that IFNs serve as potential prophylactic agents to treat corona viral infections and provided information on the safety and targeted period that needs to be carefully monitored before recommending them as standard therapies. Persistent IFN response may stimulate many ISGs, which can induce antiviral state in responsive cells but may also induce apoptosis and fibrosis and thereby cause immunopathology. Timing and dose adjustment while using recombinant IFNs may reduce side effects and control SARS-CoV2 infection and COVID-19 pathogenesis [41]. In summary, to minimize COVID-19 morbidity and mortality, there is still a significant need to develop effective therapies to limit viral infection and dampen cytokine-mediated inflammatory response . Future studies may focus on developing prophylactic and treatment strategies to prevent SARS-CoV2 infection with small molecule drug candidates and IFNs while reducing lung inflammation.

5. Role of cytokines in inflammatory responses induced by SARS-CoV2 infection in COVID-19 patients

A large body of evidence suggests that cytokine mediated inflammation plays a major role in COVID-19 pathogenesis [7,8]. IL-6 was identified as a major regulator of SARS-CoV2 induced inflammation. Therefore, IL-6

antagonism was suggested as a novel therapy to treat critically ill COVID-19 patients with significantly elevated IL-6 levels [61,62]. A study conducted in 134 ICU patients treated with tocilizumab, a humanized IL-6 receptor antagonistic monoclonal antibody, showed 10% lower mortality rate compared to those that did not receive therapy [63]. This study has demonstrated that reduced inflammation during SARS-CoV2 infection may recover patients and may decrease disease severity. However, in Roche's phase III COVACTA study of tocilizumab (Actemra/RoActemra), though time to discharge COVID-19 patients was eight days shorter in tocilizumab treated patients as compared with placebo, no difference was observed in their clinical status (https://www.roche.com/investors/updates/inv-update-2020–07–29.htm). Patient selection criteria should include higher IL-6 levels before recruitment; otherwise, these studies will generate results that are difficult to interpret and could fail to derive a therapeutic outcome. "The right patient, right timing, and right therapy" may work well to investigate novel therapies. In addition to reduced levels of IL-6, CRP, and serum ferritin may potentially predict reduced inflammation and serve as important biomarkers. These considerations based on biomarkers should be included in the selection criteria for patients to enroll in studies testing these novel therapies [64]. Mast cells (MCs) play a major role in allergic reactions and are important source of cytokines in lung tissue. Cytokines produced from MCs following respiratory viral infections may regulate inflammatory response in lung tissue [65]. Following SARS-CoV2 infection, TLR mediated MC recruitment and further accumulation of MCs in large numbers in the lung may exacerbate lung inflammation [66,67]. Several studies have shown that IL-6 and fibrinogen are important predictors of COVID-19 prognosis and contributes to systemic inflammation and higher mortality rate [68]. The binding of SARS-CoV2 to the TLR resulted in the release of pro-IL-1β which is further cleaved by Caspase-1 to produce active form that is involved in lung inflammation. Activated IL-1β is responsible for fever and induction of fibrotic pathways and may cause severe respiratory problems and ARDS [69,70]. IL-37 produced by natural killer cells, activated B cells, monocytes, keratinocytes and epithelial cells suppresses innate and acquired immune responses and downstream signals mediated through inhibition of MyD88 may reduce synthesis of IL-6, IL-1β, TNFα and CCL2 cytokines [71,72]. In addition, IL-38 produced by B cells and macrophages inhibits IL-1β and thereby inhibits inflammation caused by SARS-CoV2 infection [69]. Anti-inflammatory effects of IL-37 and IL-38 cytokines were implicated in suppression of inflammatory responses observed during SARS-CoV2 infection.

6. Role of TLRs in regulating interferon and inflammatory responses during coronaviral infections

Viruses, bacteria, fungi, and parasites contain unique molecular structures called Pathogen Associated Molecular Patterns (PAMPs). Pattern Recognition Receptors (PRRs) expressed in human cells recognize PAMPs such as the unique sequence in RNA/DNA, carbohydrates and lipids [73]. Interaction of PAMPs with TLRs, a unique group of PRRs initiate antiviral response to limit viral infection through induction of type I and III IFNs and inflammatory mediators [73]. Excessive activation of TLRs, STAT1 and NF-κB pathways primarily regulate inflammation during corona viral infection [74,75]. TLR ligands that mimic PAMPs may induce potent IFN response and serve as therapeutic agents against several highly pathogenic viruses, including SARS, MERS and COVID-19 [74]. However, TLR signaling leads to the downstream synthesis of IL-1β, IL-12 and TNFα, critical mediators of inflammation (Fig. 2). Human cells express ten different TLRs. TLR3/7/8/9 are localized to endosomal compartments to interact with unique sequences or motifs present in viral RNA and this signaling cascade is depicted in Fig. 1 [76,77]. TLR signaling is immediately activated upon virus infection and regulates virus-specific adaptive immune responses, which

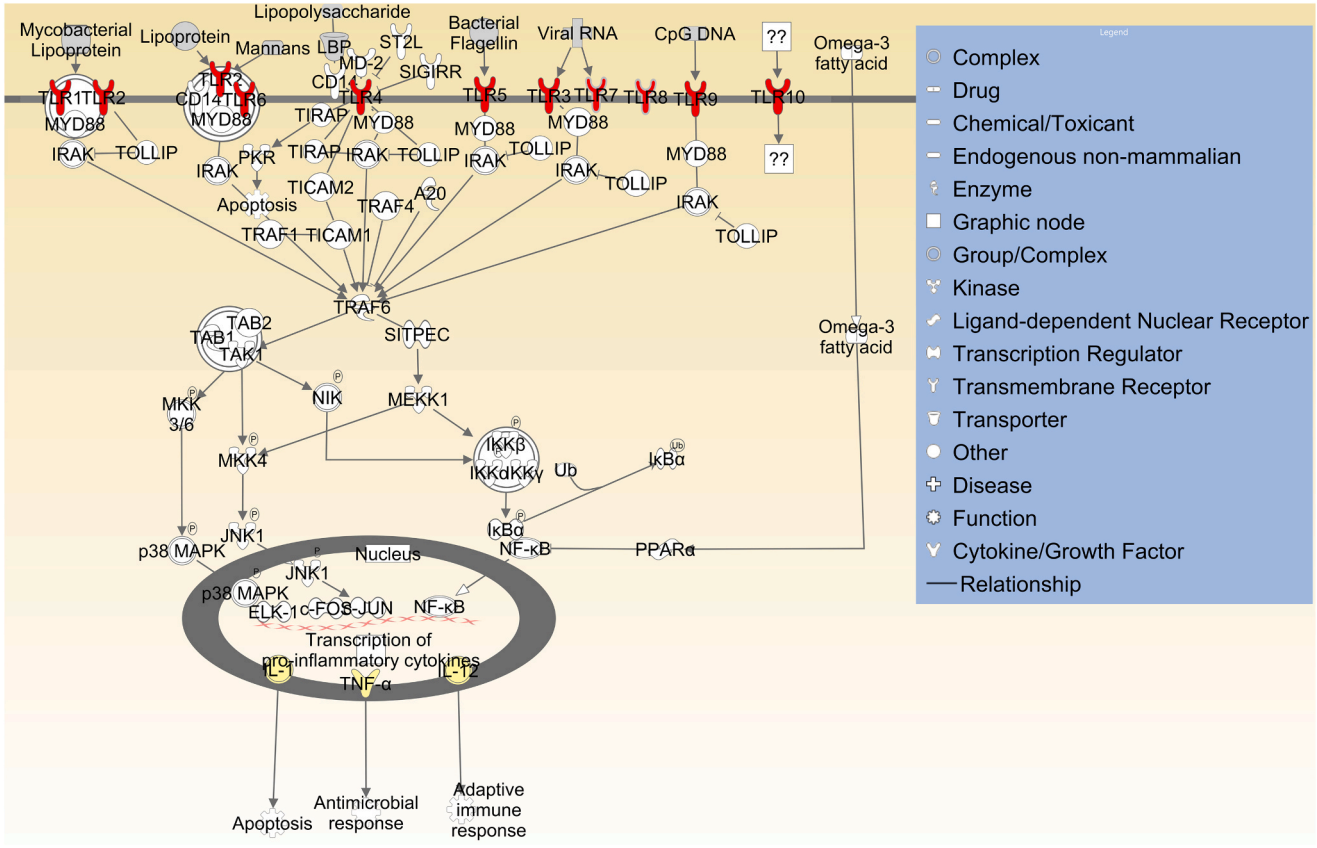

Fig. 2. Toll-like receptor-mediated induction of pro-inflammatory mediators that stimulate apoptosis, a type of programmed cell death, antiviral response, and adaptive immune responses.

plays a pivotal role in reducing viral infection [74]. Triggering of TLR signalling will produce chemokines that attract selective immune cells to the site of infection thereby controlling the viral load in the host. Compared to SARS-CoV and MERS-CoV infections, SARS-CoV2 exhibits faster human-to-human transmission [74]. Genetic variability among corona viruses may explain these differences in TLR mediated cytokine induction. Sequence motifs in SARS-CoV2 genomic RNA such as UU (U/C) and UU(G/A) motifs (moderate binding) are recognized by TLR7/8 and thereby induce pro-inflammatory responses [78]. The total number of UUU and UUA rich sequences in the SARS-CoV2 genome are higher (706 and > 873) as compared with SARS (603 and 689) and MERS (655 and 791) genomes [78]. In contrast, less number of UUC sequences were observed in SARS-CoV2 (518) as compared to SARS-CoV (563) or MERS-CoV (581) [78]. High numbers of UUU/UUA motifs may contribute to heightened pro-inflammatory cytokine response during SARS-CoV2 infection but needs further investigation.

7. TLR7/8 agonists as potential therapeutics to treat coronaviral infections

TLR7 is constitutively expressed in pDCs and B cells [79]. A low amount of TLR7 is also expressed in epithelial cells, hepatocytes and keratinocytes [80,81]. TLR8 is highly expressed in monocytes, macrophages, myeloid DCs (mDCs) and only modestly expressed in pDCs [82]. Myeloid Differentiation primary response protein (MyD88) mediated pathways are induced following interaction of TLR7/8 with viral RNA [83]. Agonistic molecules interact with TLR8 receptors present in mDCs and monocyte derived DCs (MD-DCs) and induce production of interleukin 12 (IL-12), Tumor Necrosis Factor α (TNFα), and Macrophage Inflammatory Protein-1α (MIP-1α) [77]. Imidazoquinoline, a tricyclic organic molecule such as imiquimod [R837] and resiquimod are potent small molecule agonists of TLR7/8 pathways [84,85]. TLR7 agonists activate pDCs and monocytes, which induce a signaling cascade to produce IFNα/β [51,86]. In previous studies, TLR7 agonists were used as antiviral therapeutics to generate potent type I IFN response [87,88]. For example, imiquimod, also called Aldara or R-837 is the first FDA approved topically active TLR7 agonist to treat genital warts. Imiquimod activates pDCs to produce type I IFNs and was successfully used to treat human papillomavirus (HPV) infection-induced genital warts and is a therapeutic agent for basal cell carcinoma [94]. In a two randomized, double blind phase IIa studies, oral administration of resiquimod (0.02 mg/kg), a TLR7/8 agonist, twice a week for four weeks was well tolerated and induced IFNα production and thereby reduced hepatitis C virus (HCV) infection [89]. Resiquimod may have anti-inflammatory effects, which is evident from “in vitro” experiments in which stimulation of monocytes derived from HIV-infected persons with resiquimod produced significantly less TNFα than those derived from healthy controls providing the evidence on reducing the inflammation with TLR7/8 agonists [95]. TLR7 stimulation in the airways has the potential to reduce responses to aeroallergens by induction of type I IFNs. For example, GSK2245035, TLR7 agonist was tested in a randomized, double blind, placebo-controlled study (TL7116958) over two pollen seasons (n = 42). Participants received eight single daily doses of low (20 ng, n = 14) or high (80 ng, n = 14) or placebo (n = 14) for 8 weeks [84]. This study results showed that GSK2245035 was well tolerated and reduces allergic reactivity to nasal challenges for three weeks following treatment [84]. TLR7/8 ligands either bind to both TLR7/8 receptors or selectively interact with either one to initiate a signaling cascade. For example, imiquimod activates TLR7, whereas CL097 induces TLR7/8 mediated responses [96]. Small structural modifications in TLR7/8 agonists may result in variable TLR7/8 pathway specific responses and selective induction of IFNs and inflammatory mediators . Following induction of antiviral response, downstream products of TLR7/8 pathway may regulate adaptive and cell-mediated immune responses. For example, loxoribine, a selective TLR7 agonist, was shown to enhance tetanus-specific IgG antibody secretion in a dose-dependent manner in human PBMCs [92] and strongly activates NK cells in an IL-12-dependent manner [97]. Oligodeoxynucleotide (ODN) based TLR7/8 agonists contain a 7-deaza-dG or anabino-G modification and 2’-O-methyl-ribonuclotides [99]. Imiquimod induces production of IFNα, IFNβ, TNFα, IL-6, and IL-8 cytokines in human promonocytic cells [49]. Immunity boosting effects of TLR ligands are also utilized to improve vaccine-induced immunogenicity. 3 M-052, a dual TLR7/8 agonist, was shown to enhance the immunogenicity of influenza vaccine [98].

On the contrary, more recently, niclosamide, a helminthic drug was shown to inhibit replication of SARS-CoV, MERS-CoV in Vero cells and may have the potential to treat COVID-19 [100]. Hydroxychloroquine was tested against SARS-CoV2 infection based on it’s use in treatment of immune-mediated inflammatory response against Systemic Lupus Erythematosus, rheumatoid arthritis and Sjogren’s syndrome [90,91]. Mechanistically, niclosamide enhances the efficacy of programmed death 1/programmed death 1 ligand (PD-1/PD-L1) immune checkpoint blockade. At the same time, hydroxychloroquine and azithromycin inhibit TLR7/8 signaling [92,93] Selective interference of PD-1/PDL-1 pathway with antagonistic antibodies against PD-1 receptor reduces type I IFN response and ISG expression in chronic HIV infection [31–33]. However, whether niclosamide mediated improvement in therapeutic benefit is associated with reduced type I IFN-mediated inflammation observed during PD-1 blockade remains unknown. TLR7/8 agonist-mediated induction of IFN response is important to limit viral infection, but sustained use may trigger a pro-inflammatory microenvironment thereby leading to virus induced tissue damage. Following SARS-CoV2 infection, type I and III IFNs are induced in peripheral blood or lung tissues and in gut. Lamers et al. showed that SARS-CoV2 infection of human small intestinal organoids (hSIOs) produce high amount of type I and III IFNs [7]. ISGs that are downstream to TLR7/8 pathways are highly induced upon SARS-CoV2 infection [7]. Unlike SARS-CoV, SARS-CoV2 initially induces a stronger type I and III IFN response. Production of highly potent ISGs such as IP10 (CXCL10), ISG15 and low levels of IFNβ1 at a later stage may contribute to cytokine storm either by chemo-attracting inflammation-inducing immune cells or causing tissue damage [8]. To regulate pro-inflammatory responses, balancing the hyperactivation of TLR7/8 pathways with modulators is an important approach, which may potentially treat the cytokine storm observed in lung, gut and other tissues in severely infected COVID-19 patients.

8. Conclusion

SARS-CoV2 infects the lung, heart, gut, and several anatomical sites in the body of COVID-19 patients. The robust and immediate response of the innate immune system against SARS-CoV2 infection releases IFNs and produces high amounts of pro-inflammatory mediators. Antiviral activity of type I IFNs limits SARS-CoV2 infection, whereas a persistent cytokine storm causes tissue damage and organ failure. TLR7/8 receptors recognize RNA motifs localized to the genomes of coronaviruses to initiate type I and -III IFN responses. Coronaviruses have developed several strategies to evade host-mediated antiviral IFN responses. Data suggest that a lower IFN-I and -III response was observed in PBMCs of SARS-CoV2 infected persons, and a higher ISG expression was observed in lung and gut tissues. However, mechanisms that contribute to these compartmentalized type I and III IFN responses remain unclear. TLR7/8 agonists induce potent type I and III IFN and cytokine responses, which may have the ability to limit SARS-CoV2 infection and may be an important therapeutic approach either alone or in combination with antiviral drugs to treat COVID-19 patients. Recombinant IFNs and agonistic TLR7/8 ligands are potential therapeutics to prevent and treat COVID-19. During these therapies, control of inflammation to mitigate the viral infection’s detrimental effects is important to achieve therapeutic benefit. Further evidence on clinical evaluation of TLR7/8 agonists may develop effective therapeutic options to effectively treat SARS-CoV2 infection in COVID-19 patients. Similarly, a thorough

investigation of inflammatory response in patients with post-COVID-19 complications will be a useful strategy in tailoring effective treatment approaches.

Author contribution

S.R.D and D.B.S. performed the literature search and developed the hypothesis. S.R.D. and D.B.S. wrote the manuscript. R.S, R.E, G.P.P, V.D. C, S.N.A, C.V.F, and A.T.P helped in the preparation of the manuscript. All authors reviewed the manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interests.

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