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Roles and Functions of Toll-Like Receptors in Coronavirus Infections: Forthcoming Vaccine and Therapeutic Strategies for Confronting COVID-19

Azadeh Zahmatkesh[1], Masoumeh Bagheri[2]*

[1]Department of Anaerobic Bacterial Vaccine Research and Production, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran. [2]Department of Animal Viral Vaccine, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran.

A R T I C L E I N F O

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***Corresponding Author:**
Masoumeh Bagheri
Department of Animal Viral Vaccine, Razi Vaccine and Serum Research Institute (RVSRI), Agricultural Research, Education and Extension Organization (AREEO), Karaj 3197619751, Iran.
Email: m.bagheri@rvsri.ac.ir
Tel/Fax: +98-26-34581009/ +98-26-34552194

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A B S T R A C T

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) that detect pathogen associated molecular patterns and activate innate and adaptive immune system. Coronaviruses can be detected via TLRs through their biological materials such as ribonucleic acids, glycoproteins and CpG motifs. During COVID-19 pandemic, different strategies have been used for combating SARS-CoV-2 to initiate a proper and balanced immune response through TLRs or other PRRS. Understanding the trigerred TLR signaling pathways during coronavirus infections would assist to understand the control and defense mechanisms against these viral diseases. In this review, we summarize different studies on the use and function of of TLRs and their signaling pathways as vaccines/adjuvants or therapeutic agents against coronavirus infections. Since the pandemic is ongoing and there still many unknowns with respect to COVID-19 immunology, we highlight the role of TLRs and their agonists/antagonists in previous coronavirus infections, and show their potential role in the current SARS-CoV-2 immunopathology.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease-19 (COVID-19), was reported in Wuhan, China in December 2019 for the first time [1]. To confront this disease, some products have so far received certificates of approval (e.g., vaccines manufactured by Pfizer-BioNTech , Oxford-AstraZeneca, Sinopharm, Moderna, etc.) and some are waiting in line for the license (e.g., Zydus Cadila). Although, new promising vaccines and therapeutics have been released in some countries, there still are concerns about their immunogenicity and side effects. Therefore, research in this area is still ongoing. Toll-like receptors (TLRs), which are needed for activation of innate immunity and initiation of adaptive immunity, have been considered in several studies on respiratory diseases such as influenza, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) [2-7], and also, in some limited studies in the recently-emerged COVID-19 [8, 9].

In this review, we have focused on all TLRs involved in coronaviruses or other respiratory-related infections to find similar features between their behaviors and those of COVID-19, in order to pave the way for emergence of new vaccines or therapeutic strategies. We believe that successful application of TLRs agonists/antagonists in some experimental or trial vaccines or drugs for respiratory diseases may assist the forthcoming studies on COVID-19. The following is a summary of multiple studies related to TLRs and their signaling pathways as vaccines/adjuvants or therapeutic agents for SARS-CoV-2 infection.

Biology of TLRs

The innate immune system employs germline-encoded pattern recognition receptors (PRRs) for initial recognition of microbes [10]. TLRs are a class of PRRs that detect pathogen associated molecular patterns (PAMPs), activate the innate immune system [11] and are vital for commencement of the adaptive immunity [12]. TLRs are encoded by a multi-gene family, expressed on the surface of dendritic cells, macrophages, and neutrophils [13, 14]. They are composed of an extracellular domain (ECD), a short transmembrane segment and an intracellular Toll/Interleukin-1 receptor (TIR) signaling

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domain [15]. The cytoplasmic segment of TLRs, (TIR domain), activates the TLR signaling pathway [16].

The ECD has a 3D horseshoe-like structure containing leucine-rich repeats (LRRs). Generally, ECD consists of N-terminal, central, and C-terminal sub-domains [17, 18]. Ligand binding to TLR leads to homo- or hetero-dimerization, forming an M-shaped complex where the two C-terminal domains converge in the middle [19, 20]. This conformation activates a signaling pathway, inducing myeloid differentiation primary response 88 (MyD88) as a TIR domain-containing common adaptor, resulting in activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interferon regulatory factor (IRFs), or MAP kinases to control the expression of cytokines, chemokines, and type I interferon (IFN) that protect the host against microbial infections [21, 22]. However, previous studies have shown that individual TLRs have their own signaling molecules to manifest specific responses [23]. Other adaptor proteins include MyD88 adaptor-like protein (Mal)/ TIR domain-containing adaptor protein (TIRAP), TIR domain-containing adaptor protein inducing interferon-β (TRIF)/TICAM and TRIF-related adaptor molecule (TRAM) [24]. TLR-mediated recognition of microorganisms induces phagocytosis and presenting of antigens to T lymphocytes through major histocompatibility complex (MHC) molecules [12]. TLRs are expressed on the cell surface (TLR1, TLR2, TLR4, TLR5 and TLR6) or on intracellular membranes of the endosomes (TLR3, 7, 8, and 9). The endosomal TLRs recognize viral or bacterial nucleic acids [25, 26].

Coronaviruses and the Host Immune Response

Beta coronaviruses are positive-sense single-stranded RNA (ssRNA) viruses. After internalization in the host cells, their genomic material works as messenger RNA, and is translated to viral structural proteins, which are involved in viral replication and transcription [8, 27, 28]. Coronaviruses are highly pathogenic in humans and lead to respiratory infections such as MERS, SARS and the recent COVID-19. The virion of coronaviruses consists of a bilayer lipidic membrane (viral envelope), and an RNA genome protected inside protein-based nucleocapsids. The viral envelope is made of phospholipids, proteins and glycoproteins and may help the virus to elude the host immune system. Its surface glycoproteins are thought to link to receptors on the host cell membrane [8, 28, 27]. Due to the lymphocytopenia and cytokine storm syndrome, coronavirus may escape the immune system, which may result in increased pathogenicity. The severity of all types of coronaviruses is highly related to elevated levels of leukocytes, proinflammatory cytokines and up-regulation of type I interferon (IFN) [29-31, 1, 32-34]. Although activation of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) during infection is effective in controlling the viral dissemination, it has also some negative effects for the hosts (e.g., pathological damage of the tissues) [35]. Understanding the triggered TLR signaling pathways during coronavirus infections will shed light on the control mechanisms of these viral diseases. It has been proposed that binding of SARS-Cov-2-associated PAMPs to the TLRs initiates the immunological response against COVID-19 [36], while lethal consequences are also the result of these interactions [37, 38]. TLRs involved in some viral respiratory diseases, including coronavirus infections are summarized in Table1.

Table 1. TLRs involved in some viral respiratory infections, their agonists, antagonists and associated studies.

TLR	Related studies on respiratory infections	Agonist	Studies on agonists/respiratory infections	Antagonist	Studies on antagonists/respiratory infections
TLR1	SARS-CoV, SARS-CoV-2	-	-	-	-
TLR3	West Nile virus, SARS-CoV-2	poly I:C	MERS-CoV, SARS-CoV, Influenza virus	-	-
		rintatolimod	MERS-CoV, SARS-CoV		
TLR4	MERS-CoV, SARS-CoV, SARS-CoV-2	LPS	SARS-CoV	Eritoran	Influenza virus
TLR5	SARS-CoV- 2	Flagellin	H7N9 influenza, West Nile virus	-	-
TLR6	SARS-CoV, SARS-CoV-2	PUL042	SARS-CoV-2	-	-
TLR7	MERS-CoV, SARS-CoV, SARS-CoV-2	R484	SARS-CoV	M5049	SARS-CoV-2
		Imiquimod	Influenza viruses		
TLR8	MERS-CoV, SARS-CoV, SARS-CoV-2	R484	SARS-CoV	M5049	SARS-CoV-2
		Imiquimod	Influenza viruses		
TLR9	SARS-CoV, Avian infectious bronchitis virus, Bovine coronavirus, Human coronavirus 229E	CpG	SARS-CoV	-	-
		PUL042	SARS-CoV-2		

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TLRs Triggered during Coronavirus Infections

I) Endosomal TLRs

Endosomal TLRs (TLR3, 7, 8 and 9) along with TLR4 can detect viral nucleic acids and are crucial for the initiation of antiviral immune responses [39]. TLR3 binds to viral double-stranded RNA (dsRNA) and TLR7/8 bind to viral ssRNA [3]. In SARS-CoV, the major PAMPs are proposed to be the ssRNA and the spike protein. When TLRs detect PAMPs, innate immunity begins the functions that involve the secretion of IFNs and inflammatory cytokines and chemokines to combat the viral replication and spreading [3]. Although, the activity of these immunologic messenger molecules is crucial to protect the host against the infections, the up-regulation and exhaustion of the adaptive immune system, is the major reason of the cytokine storm in severe cases of COVID-19 [40]. Acidic environment of endosomes is the prerequisite for the antiviral effectiveness of the endosomal TLRs against coronaviruses [3, 41]. Chloroquine and hydroxychloroquine have been proposed as potential drugs against COVID-19 due to in vitro data showing their antiviral activity against different viruses such as coronavirus [42]. However, the antiviral effects of these drugs are established in more basic environments, which may limit the desirable effect of TLR function, and damage the body's natural defense system. Therefore, it has been noted that the prescription of chloroquine for COVID-19 patients, may have a reverse/damaging effect, especially for the immunosuppressed individuals [40].

Recognition of a viral pathogen by TLRs triggers one of the two different adaptor molecules, namely MyD88 (MyD88-dependent pathway) or TRIF (MyD88-independent pathway). In the next step, these molecules activate the mitogen-activated protein kinases (MAPK) and nuclear factor-κB (NF-κB) molecules [11, 43]. The MyD88-dependent pathway results in entry of activated NF-κB into the nucleus and induction of gene expression of proinflammatory cytokines such as IL-6 and TNF-α. [44]. The MyD88-independent pathways, induces the expression of IFN-γ and IFN downstream genes [13]. Induction of TLR3 activates MyD88-independent signaling pathways, which induces the expression of IFN-γ and IFN downstream genes [13]. TLR3 involves TRIF as an adaptor [45]. TLR3 has been reported to detect the West Nile virus, which is an ssRNA virus, in a rodent model [46]. TLR3 induces interferon regulatory factors (i.e., IRF7 and IRF3) after activation by its ligand [47]. Recent studies on the design of vaccines using multi-epitope peptides of SARS-CoV-2 antigenic proteins have shown strong binding to human TLR3, which are suggested for induction of the immune responses against SARS-CoV-2 [5, 48].

During influenza infection, cytokines are expressed in lung epithelial cells, macrophages, and dendritic cells through function of TLR3, TLR7, and TLR8, retinoic acid-inducible gene I, and the NOD-like receptors [49]. Cytokine storm occurs in severe conditions of COVID-19, similar to influenza infection. However, there is scant information on immunopathology of COVID-19. It has been suggested that blocking one of the proinflammatory cytokines (such as by anti-IL-6R monoclonal antibody) may reduce the inflammatory reaction [50]. However, it seems that IL-6 is important for initiation of the immune response against viral infection since IL-6 or IL-6R deficiency has resulted in persistence of influenza infection in mice [51].

An immunoinformatic study on the SARS-CoV-2 genome has shown the probability of interaction of TLR7/8 with MERS-CoV genome. However, SARS-CoV-2 genome had more ssRNA motif fragments detectable by TLR7/8, compared to SARS-CoV genome, indicating higher probability of interacting with TLR7/8. This finding implies the potential ability of SARS-CoV-2 to induce proinflammatory reactions through TLR7/8, leading to acute lung injury and death [9]. In vitro studies have suggested that unusual type I/III IFN responses due to TLR7 genetic mutation in some SARS-CoV-2-infected families are specifically related to a severe COVID-19 [52].

Both TLR7 and 8 are encoded by the X chromosome [53], and are supposed to be associated to SARS-COV-2 gender-related risk factors. In humans, TLR7 is prominently expressed on the endosomal membranes in plasmacytoid dendritic cells (DC) and B lymphocytes. TLR8 is expressed in monocytes and neutrophils [54] while cells expressing TLR7 [55] and TLR8 [56, 57] are highly present in the lung tissue. TLR7-positive plasmacytoid DC can produce high amounts of type I interferon after induction by influenza virus [2]. Murine TLR7 and human TLR8 are involved in species-specific detection of GU-rich ssRNA oligonucleotides, derived from human immunodeficiency virus-1 (HIV-1) [56]. TLR7 and/ or 8 pathways stimulated in immune responses may have also undesirable side effects. Occurrence of cytokine storm leading to up-regulation of inflammatory cytokines such as IL-6 and TNF-α has been reported in respiratory disorders/infections such as asthma [58], SARS-CoV-1 [29] and SARS-CoV-2 [1]. Females have two X chromosome, one of which is inactivated in each cell [59]. However, TLR7 and probably TLR8 genes evade transcriptional silencing; hence, the genetic information of both alleles is expressed. In males, only one copy of the X chromosome exists [60], Therefore, different expression profile resulted from gender-associated X inactivation may cause females more potent to induce immune response against single-stranded viruses such as SARS-CoV-2 [61]. The cytokine storm is responsible for lung tissue damage and destructive outcomes of COVID-19 infection. Since, IL-6 level in male patients is higher than in women, it is assumed to have an important role in the cytokine storm [62]. However, in healthy people, it has been demonstrated that the expression of IL-6 in monocytes was higher in women compared to men [63]. It seems that the higher IL-6 level in normal women acts more effectively in initial stages of detection of SARS-CoV-2 compared to men; however, the acute rise in IL-6 level in men during the viral infection results in adverse effects. Finding a clear relationship among sex, TLR7/8 gene expression and IL-6 activation in healthy people versus the patients would give beneficial information on mechanisms of the immune responses in viral sepsis cases.

There are reports on various copy numbers of TLR7 and 8 mRNA in the population [64], and single nucleotide polymorphisms in TLR3, 7 and 8 genes [64, 65], that may affect the interaction of TLRs with their ligands and their downstream signal transductions [61]. Probably, the early detection of virus and on time innate and adaptive immune responses against the virus decrease the viral load and can protect the host body from the cytokine storm, reported mostly in male humans [30, 66, 67]. TLR3 induces an interferon regulatory transcription factor (IRF)3-mediated type I IFN response and an NF-κB-mediated pro-inflammatory response. Mutations in TLR3 have been associated with disease severity in COVID-19 patients [68]. In the peripheral blood, the gene expression profiles of TLRs 3, 4, 7, 8, and 9 have been determined along with measuring the level of circulating

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cytokines in plasma in COVID‑19 mild and severe groups. The sever group are showed to have TLR4 overexpression and lower expression of TLR3. This was associated with negative consequences in severe COVID‑19 patients [69].

TLR9 is an intracellular TLR, detecting bacterial and viral DNA molecules. It has been known that TLR9 responds to CpG signaling motifs (GTCGTT) [70, 54]. In a human in vitro study of SARS-CoV infection, expression of CD14, TLR9, FKβ1 and GATA signaling increased as evidences of monocyte-macrophage activation. It has been reported that TLR9 was highly expressed in response to SARS-CoV infection, likely through viral CpG signaling motifs, in comparison to TLR2 and TLR4, indicating its specificity for the virus. SARS-CoV viral sequence has significantly more signaling motifs (7 copies) than some other viruses involved in respiratory diseases, and the highest number compared to other coronaviruses (Human coronavirus 229E, Murine hepatitis virus, Avian infectious bronchitis virus and Bovine coronavirus). TLR9 is supposed to help detection of the virus through CpG motifs and initiation of the innate immunity ([71]).

II) Cell-Surface TLRs

TLR4 use both MyD88- and TRIF-dependent signaling pathways to induce downstream molecules [19], which finally lead to induction of expression of proinflammatory cytokines [72] or IFN-γ and IFN downstream genes [73]. It has been reported that TLR4-deficient mice experience more severe SARS-CoV infections than wild-type mice, suggesting that TLR4/TRIF signaling pathway might have a protective effect against some coronaviruses [4]. In SARS-CoV-2, the spike protein binds to TLR4 with high affinity in vitro, and stimulates a TLR4-dependent IL-1β response [74].

The chronic inflammatory responses in COVID-19 patients with cardiometabolic diseases is associated with the overexpression of proinflammatory cytokines such as IL-6 and TNF-α [75], which are downstream of the TLR4 signaling pathway [76]. The transcript expression of TLR4 and its downstream signaling molecules (MYD88, TRAF6, TIRAP, CD14, IRAK1 and TICAM) has been studied in COVID-19 patients, which showed upregulation compared with healthy controls. These results have led to the conclusion that activation of TLR4-mediated NF-κB signaling pathway is associated with the upregulation of inflammatory responses in COVID-19 patients. No significant differences were observed in the expression of other TLRs (i.e., TLR3, TLR7, TLR8, and TLR9), between COVID-19 patients and the healthy controls [77].

A SARS-CoV-2 spike subunit vaccine formulated with dual TLR4/TLR7/8 agonist liposome adjuvant has been developed. The adjuvanted vaccine induced systemic neutralizing antibodies and anti-Spike IgA, and protected mice against lung injury upon a challenge [78]. Proinflammatory cytokines such as IL-1β, IL-6, and TNF-α are mainly expressed by monocytes, macrophages and non-immune cells. They have a pivotal role in elimination of viral infections by up-regulation of inflammatory responses and stimulation of innate and adaptive immunity [79]. Irregular stimulation or imbalance of proinflammatory cytokines may result in severe systemic inflammatory reactions and organ damage [80]. In an in vitro study, it was shown that the spike protein of MERS-CoV interacts with DPP4 (a macrophage receptor) and reduces the production of proinflammatory cytokines such as TNFα and IL-6 in macrophages. Moreover, it induces the expression of some negative regulators of the TLR4 signaling pathways, which result in down-expression of IFN-α and IFN-β [7]. Long-term persistence of negative regulators impairs the defense against MERS-CoV infections [19]. In vitro and in vivo studies have shown that TLR2 senses the SARS-CoV-2 envelope protein as its ligand, resulting in MyD88-dependent inflammation and production of proinflammatory cytokines. Also, blocking of TLR2 signaling have led to protection against the pathogenesis of SARS-CoV-2 infection [81].

An in silico study on the interactions of SARS-CoV-2 spike glycoprotein with the host receptors has indicated a close relationship between bat SARS-CoV and SARS-CoV-2 spike protein and its receptor ACE2 and also a few TLRs (TLR1, 4, and 6). The interaction of spike protein with TLR4 was found so strong that selective targeting of TLR4-spike protein interaction by designing competitive TLR4-antagonists was suggested as a therapeutic strategy and a potential treatment for COVID-19 [6]. The first study showed that dysregulation of TLR4 damages the defensive mechanism against MERS-CoV. Nevertheless, the second study proposed that down-regulation of TLR4 would be a helpful treatment against SARS-CoV-2. Summing up these seemingly contradictory findings confirms the two-aspect characteristic of proinflammatory cytokines and/or TLRs. While they are needed for detection of the virus and initiation of the immune response, hyper-expression of the proinflammatory cytokines impairs a normal immune response, and probably is needed to be blocked. Proinflammatory responses induced by activation of TLRs are the first line of host immunity, which help to remove the pathogen and to restore the immune homeostasis [82]. However, dysfunction of TLRs results in several immunopathological outcomes such as sepsis or cytokines storm, observed in coronavirus infections.

One of the major causes of TLR dysregulation is the mutation in TLRs genes [83, 43, 84, 85], which may affect the interaction of TLRs with their ligands, impairing the host normal immune responses [86]. TLRs are typically under purifying selection with signatures of positive selection, mostly in cell-surface TLRs rather than in intracellular TLRs. This indicates the conserved feature of the viral pathogens, detected on intracellular TLRs, compared with the escaping bacterial pathogens, detected on the cell surface TLRs [87]. Nevertheless, for coronaviruses, studies have shown that different (cell-surface or endosomal) TLRs are triggered.

What Would be the Best Strategy: TLR Agonists or Antagonists?

Concerning COVID-19 pandemic, it should be kept in mind that two different strategies are needed for combating SARS-CoV-2. Namely, one as a vaccine for "the uninfected individuals" to initiate a proper immune response through TLRs, and the other as a drug for "the severely-infected patients" to ameliorate the destructive effects of the proinflammatory cytokines (Fig. 1). Application of TLR agonists and antagonists are the main examples of these strategies that have been studied and are undergoing their trials [88] (Table 1).

TLRs can induce antiviral mechanisms to combat viral diseases, and this effect can be mimicked by agonists of TLRs, especially in cases where viruses have disturbed the regular activity of TLRs [89]. Adjuvants that induce TLR pathways through both MyD88 and TRIF routes may have a synergistic effect on the host defense, particularly when both are critical to the host immune response, such as in SARS-CoV infection [4].

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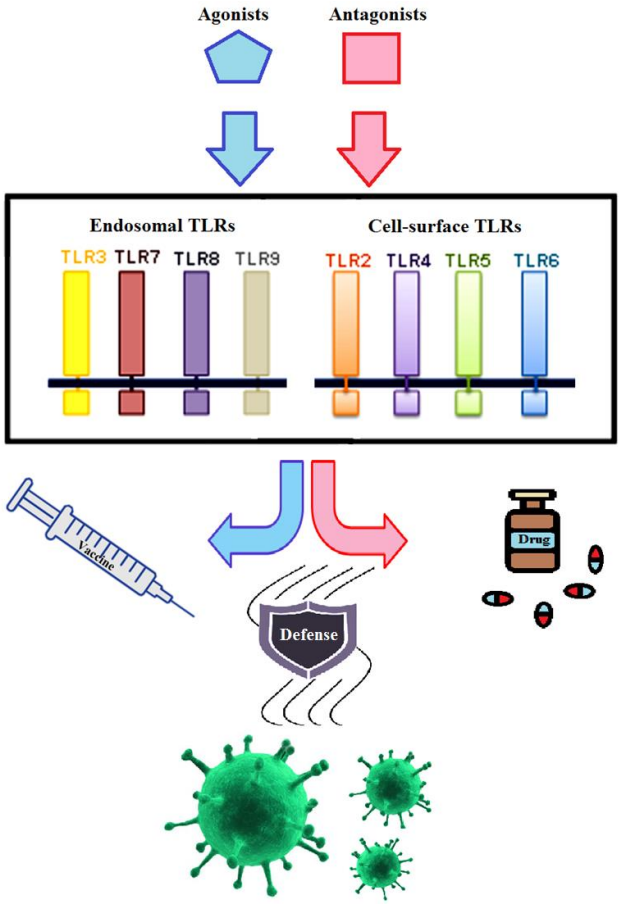


Fig. 1. Two defense strategies triggering TLRs for fighting against SARS-CoV-2.

TLR Agonists Used in Vaccine Development

Polyriboinosinic:polyribocytidylic acid (poly I:C) is a synthetic analog of dsRNA and is a TLR3 agonist which has been introduced as a potential vaccine adjuvant for MERS-CoV in a mouse model [90]. Poly I:C induces type 1 interferon expression (IFN-β and IFN-α) [91], resulting in stimulation of antiviral functions of natural killer (NK) cells, CD8 T-cells, and macrophages [92, 93]. It has also been suggested that application of TLR4 and TLR3 agonists as adjuvants along with MERS CoV-Spike protein could be an effective way to enhance immunity against MERS-CoV infection [94]. Poly I:C has been extensively used as an effective adjuvant for controlling the coronaviruses ([95]), influenza virus [96], Hepatitis B virus [97], and some HIV strains [98]. Inoculation of poly I:C to elderly mice through nasal route has been successful in neutralizing a lethal dose of SARS coronavirus and has enhanced the animals' survival rate [99]. TLR3- poly I:C interaction leads to the initiation of adaptive immunity through induction of DC maturation, type I IFN and inflammatory cytokine/chemokine production, NK cell activation, and virus-specific T-cell responses [100]. Agonists for TLR3 (poly I:C), TLR4 (LPS), TLR7/8 (R484), and TLR9 (CpG) have been administered in aged mice before infection with SARS-CoV, and have increased the survival rate as observed for all agonists, although only poly I:C was completely protective [99]. Also, poly I:C has been shown to improve influenza vaccine protection in a mice population in the absence of pre-existing immunity [101].

TLR5 recognizes only protein ligands of the pathogens. Since TLR5 is expressed on many types of epithelial cells such as intestinal, respiratory, and kidney/urogenital tracts and ocular surfaces [102], it is thought to have a crucial role in host immunity in mammalian species. TLR5 is expressed in different immune cells such as dendritic cells, macrophages, monocytes and also on the respiratory epithelium cells and pneumonocytes in humans [103]. While encountering respiratory pathogens, TLR5 induces the signaling pathways leading to protective immune responses. Since, respiratory and pulmonary problems is a common symptom of COVID-19, it seems that TLR5 may have the ability to initiate innate immunity in the host. Bacterial flagellin is the TLR5 ligand and TLR5 stimulation through flagellin (fliC) or similar molecules (probably viral glycoproteins) may improve the immune response against the viral pathogen [104]. Flagellin has been used in some experimental viral vaccines to increase the immunity against the virus. In a study on H7N9 influenza subunit vaccines, it was shown that fliC improved the potency of hemagglutinin (HA)–nasal vaccine with enhanced humoral, cellular and local mucosal immunity in mice and chicken models [105]. Also, fliC-HA-immunized chickens challenged with H7N9 virus, showed strong immune responses, leading to decreased viral loads of throat and cloaca. In another study using primates, flagellin added to a killed influenza vaccine improved long-term antibody response against the virus in newborn monkeys [106]. Moreover, in a mouse-model study, Salmonella flagellin was suggested as a promising adjuvant against influenza virus, which was able to reduce influenza-A virus load in the lung [107]. There are several other viral vaccines targeting TLR5 such as West Nile virus vaccine [108] and Lentiviral vaccine [109]. These studies provide a basis for considering TLR5 modulation as a potential vaccine/adjuvant which could be extended for investigation on mucosal immune responses during SARS-CoV-2 infection.

TLR7 and TLR8 along with other PRRs play a significant role in defending the host against viral infections. Imiquimod is a non-nucleoside heterocyclic amine, which belongs to the class of 1H-imidazo-[4, 5-c] quinolones [110, 111]. Imiquimod is a TLR7/8 agonist and an immuno-stimulator that exerts its function in innate immunity by binding to cell surface receptors, especially TLR7 and TLR8. It enhances both non-specific and specific immune responses, particularly the cell-mediated pathways [112]. It is able to modify the immune response, by inducing the expression and production of a number of cytokines, which further stimulate the T-cells. Therefore, Imiquimod enhances innate and adaptive cellular immunity [111]. The induction of immunological reactions and the secretion of cytokines by Imiquimod initiate antiviral and anti-inflammatory responses against viral infections such as those caused by influenza viruses. This shows the potential role of Imiquimod in combatting other viral pathogens. There is evidence that Imiquimod via TLRs can give desirable stimulation of innate and adaptive immunities, helping the elimination of SARS-CoV-2, at least during the early stages of the viral infection [113]. Application of PUL042, which is TLR 2/6/9-agonist, is currently in phase III clinical trial for pre-stimulation of the immune response in uninfected individuals against SARS-CoV-2 [88].

TLR Antagonists Used in Therapeutic Approaches

The TLR4 ligand (LPS) is an inflammatory stimulus in acute respiratory distress syndrome [114]. It has been proposed that TLR4 stimulation after infection by respiratory viruses and

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bacteria induces cytokine storm, especially due to IL-6 activation leading to acute lung injury [115]. TLR4-deficient mice were protected against influenza virus, suggesting that inhibition of TLR4 would protect against influenza infection [116]. However, Totura et al. have obtained different results demonstrating that TLR4-deficient mice were more susceptible to SARS-CoV infection compared to the wild type mice [4]. It has been shown that the expression of TLR4/TLR2 is upregulated at 24 h after SARS-CoV infection, suggesting their crucial role in the generation of immune responses [117]. Eritoran, a TLR4 antagonist has been used as a treatment in influenza-infected mice and has shown promising results in inhibiting the lethality, improving lung pathology and clinical symptoms, and decreasing the viral titers. Thus, Eritoran is proposed as blocking reagent of TLR signaling, which blocks the cytokine storm and introduces a novel therapeutic approach for influenza [116] and possibly other infections such as COVID-19.

TLR-antagonists (such as M5049) are expected to ameliorate the proinflammatory responses in the symptomatic COVID-19 patients. M5049 is a potentially first-in-class small molecule that blocks the activation of TLR7 and TLR8 as innate immune sensors of viruses such as SARS-CoV-2. Activation of TLR7/8 causes the activation of the immune cells and inflammation. Therefore, using M5049 may prevent or improve the hyper-inflammatory responses in patients with COVID-19 pneumonia while it also may prevent progression to cytokine storm [118]. TLR antagonists can competitively block the binding of viral PAMPs to TLRs and reduce the expression of the proinflammatory cytokines without severe decrease in their basal levels to maintain the immune homeostasis [88]. However, suppressing human TLRs is a double-edged sword that can give rise to undesirable effects such as suppression of pathways, leading to the initial detection of the virus and lowering the viral load. Hence, it is worth considering the mode of action of these inhibitors in both COVID-19 patients and non-infected individuals. Also, proper optimization of dose and duration of the treatment has been advised for the success of TLR-targeted therapies [88].

In conclusion, great efforts have been made during COVID-19 pandemic in order to find multiple remedies or develop different efficient vaccines. Since, this infection is caused by an unknown virus with no previous information, other similar coronaviruses such as SARS-CoV and MERS-CoV have provided a good basis for designing effective hypotheses and immunological experiments. In this regard, focusing on multiple studies on TLRs involved in previous coronavirus infections will pave the way for understanding the biological and immunological mechanisms of SARS-CoV-2. TLR-inducers or inhibitors have been used in previous studies of different coronavirus or respiratory infections with promising results. According to the mode of function, TLR agonists are proposed as respiratory vaccine adjuvants for application in “healthy individuals”, and TLR antagonists are known as the “potential remedies for respiratory diseases” leading to lung injury after viral infections. Application of these stimulators or attenuators for the novel SARS-CoV-2, as vaccines or therapies would provide potential solutions to COVID-19 problem.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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