Journal of Experimental Biology and Agricultural Sciences

<http://www.jebas.org>

ISSN No. 2320 – 8694

ROLE OF TOLL-LIKE RECEPTORS IN CORONAVIRUS INFECTION AND IMMUNE RESPONSE

Muhammad Sarfaraz Iqbal^{1*}, Nimra Sardar², Wajiha Akmal², Rabia Sultan³, Humaira Abdullah⁴,
Maimoona Qindeel⁵, Kuldeep Dhama⁶, Muhammad Bilal^{7*}

¹Department of Biotechnology, School of Applied Biology, University of Okara, Pakistan.

²Department of Molecular Biology, School of Applied Biology, University of Okara, Pakistan.

³Department of Microbiology and Molecular Genetics, School of Applied Biology, University of Okara, Pakistan.

⁴Department of Zoology, University of Sargodha, Pakistan

⁵Department of Pharmacy, Quaid-i-Azam University, Islamabad 45320, Pakistan

⁶Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar-243 122, Bareilly, Uttar Pradesh, India.

⁷School of Life Science and Food Engineering, Huaiyin Institute of Technology, Huaian 223003, China.

Received – August 25, 2020; Revision – September 22, 2020; Accepted – October 15, 2020

Available Online October 25, 2020

DOI: [http://dx.doi.org/10.18006/2020.8\(Spl-1-SARS-CoV-2\).S66.S78](http://dx.doi.org/10.18006/2020.8(Spl-1-SARS-CoV-2).S66.S78)

KEYWORDS

Coronavirus

SARS-CoV-2

COVID-19

Toll-like receptors

Immune response

Macrophage system

Autophagy

Therapy

ABSTRACT

The emergence of a novel coronavirus referred to as SARS-CoV-2 has become a global health apprehension due to rapid transmission tendency, severity, and wide geographical spread. This emergence was started from Wuhan, China in 2019 from the zoonotic source and spread worldwide, infecting almost half of the community on this earth. Many of the receptors are involved in proceeding with this infection in the organism's body. Toll-like receptors (TLRs) play essential and protective functions from a wide range of microbial pathogens. Small setup of TLR adaptor proteins leads to activate nuclear factor kappa B (NF- κ B) and interferon-regulatory factor (IRF). Consequently, various advanced inflammatory cytokines, chemokines, and interferon reaction properties can be up-regulated. Similarly, TLR flagging works on autophagy in macrophages. Autophagy is a cell response to starvation that helps to eliminate damaged cytosol organelles and persistent proteins. It is also able to prevent the replication of intracellular pathogens. Several microbes subvert the autophagy pathways to sustain their viability. This review investigates how TLRs can modulate a macrophagic system and analyze the role of natural resistance autophagy.

* Corresponding author

E-mail: sarfaraz2250@gmail.com (M.S. Iqbal); bilaluaf@hotmail.com (M. Bilal).

Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

Production and Hosting by Horizon Publisher India [HPI]
(<http://www.horizonpublisherindia.in/>).
All rights reserved.

All the articles published by [Journal of Experimental Biology and Agricultural Sciences](#) are licensed under a [Creative Commons Attribution-NonCommercial 4.0 International License](#) Based on a work at www.jebas.org.

1 Introduction

The world health organization (WHO) officially named the first coronavirus in 2019 as the novel coronavirus 2019-nCoV on 7th January 2020. The infection was referred to as 'Coronavirus Disease 2019' (COVID-19), caused by a novel emerging severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This is a general risk posing high global health concerns to humans' well-being (Dhama et al., 2020). To respond to this situation, the government works closely with the compliance of state, neighboring, ancestral, and local communities and general welfare accomplices (Koh & Sng, 2010). COVID-19 causes serious disease in individuals of all ages with hidden clinical problems, and co-morbidities worsen the clinical outcome of this disease with an increase in mortality (Shah et al., 2020; Dhama et al., 2020). The new coronavirus has spread to about each nation on the planet since it initially developed in China toward the start of the year (Bilal et al., 2020a,b; Iqbal et al., 2020; Ki, 2020). Coronaviruses (CoVs) constitute an infectious group of RNA viruses, which cause animal diseases and affect humans. COVID-19 is firmly identified in the coronavirus group with intense respiratory disease (SARS). The virus infected around 8,000 people and killed about 800, but it was soon eradicated because most of those afflicted were ill, making it easier to monitor. Another coronavirus is Middle East respiratory syndrome (MERS-CoV), which occurred inconsistently since its first emergence in 2012 (Group, 2013). COVID-19 is different from these two viruses because the disease spectrum is broad, with approximately 80% of cases contributing to mellow disease. Numerous individuals can also transmit the disease and display no symptoms, making it significantly more challenging to control. Approximately, 20% of COVID-19 cases have so far been identified as "severe", and the actual rate of passage ranges between 0.7% and 3.4% depending on the region which accesses to major medical treatment. Chinese scientists agree that COVID-19 has transformed into two strains, one more effective than the other, which may hinder the production of immunization (Hughes, 2013).

Mammalian cells can recognize infections at different stages. For the intracellular identification of viral nucleic acid, toll-like receptors (TLRs) require early steps of the insusceptible reaction triggered during viral infection. In the last decade, significant efforts have been made to characterize TLR-3 in the antiviral response and explain the TLR-3 pathway at the atomic level as a 'major sentinel' against infection. TLR-3 has an essential role in the antiviral reaction against most diseases by its capacity to detect double-stranded RNA. Endogenous mRNA and RNA discharged from necrotic cells have been shown to activate the TLR-3 pathway (Pauli et al., 2008b). TLR-3 is extensively studied and well preserved among vertebrates. Its disposition has been established in invulnerable and non-safe cells. The usefulness of TLR3 antiviral function against certain infections has been

demonstrated. A specific subset of human dendritic cells that profoundly express TLR3 displays a superior limit regarding cross-introducing apoptotic and necrotic cell antigens after TLR3 (Akira, Uematsu, & Takeuchi, 2006). The technique of utilizing TLR-3 ligands as adjuvants in antibody treatment depends on the high articulation of TLR3 in human CD141+, mouse CD8a+ and dendritic cells (Zhao et al., 2014). TLR-3 intercedes pathogenesis, which could be identified with the intensification of the antiviral response. This analysis provides a framework on the TLR3 pathway, highlights the adverse guideline for TLR-3 movement by endogenous and infection-encoded proteins, and explores the production of evidence of TLR-3's involvement in viral pathogenesis (Alejandra Garcia-Cattaneo et al., 2012).

2 Innate immunity response

The innate immunity offers the first line of protection against pathogen attacks. The natural system cells perceive and react to pathogens through receptors that are encoded in the germline of the host. The intrinsic scaffold comprises three main parts: anatomical boundaries, humoral obstructions, and cellular obstacles. For example, the skin is a physical obstacle to prevent microorganisms from entering the body. Eyelash movement in the gastrointestinal and respiratory tract is another anatomically protected barrier. The humoral limits include synthetic preparations, such as lysozyme and phospholipase, which are contained in tears, salivation, and body fluids and prevent microscopic organisms' development. Suppose an intruder overcomes these obstacles or tissue damage occurs. In that case, intense reactions are triggered to activating the complementary mechanism, the coagulation mechanism, and producing antimicrobial properties of cytokines and different proteins. The third barrier includes macrophages, monocytes, neutrophils, natural lung cells, and eosinophils. The macrophages are an anterior host barrier component, which distinguishes pathogens through an extensive collection of extracellular and intracellular receptors/sensors. These germ-encoded receptors known as pattern recognition receptors (PRRs) distinguish pathogen-associated molecular patterns (PAMPs) shown by microbes, infections, parasites, and growths. PAMPs include miniaturized lipids, nucleic acids, proteins, lipoproteins, and glycans, which are determined by the creatures. PRRs are linked to downstream labelling pathways that trigger intrinsically safe reactions. The involvement of some PRRs can activate the inflammasomes, causing the IL-1 β and IL-18 emissions and contributing to the activation of natural barriers. Macrophages distinguish pathogens using PRR receptors such as Fc receptors and supplements. Phagocyte material can be falsified by combining phagosomes with late endosomes or potential lysosomes. If the microorganisms escape phagosomes in the cytosol, they can be targeted by autophagy (Kell & Gale, 2015; Khandia et al., 2019).

Autophagy sequesters attacking pathogens, harmed intracellular organelles, and misfolded proteins. These objectives are covered inside a two-fold membrane-bound compartment named an autophagosome, conveying its substance to lysosomes for debasement. Besides disposing of pathogens, both phagocytosis and autophagy disseminate remote material for antigen introduction, which is an underlying advance in the elicitation of versatile resistance. Presentation of macrophages to PRRs can fill in as a trigger for autophagosome arrangement. This gives a connection between macrophage pathogen acknowledgment and the actuation of intracellular host resistance. An early type of eukaryotic natural invulnerability, autophagy allows trapping and elimination of intracellular pathogens. Pathogens are attacked by autophagy hijackers but also damage intracellular organelles and misfolded proteins. In addition to removing pathogens, both phagocytosis and material conveying autophagy are eliminated to introduce antigen, which causes a crucial advance in the overall resistance. Presenting macrophages to PPR scan trigger autophagosome disposition (Lu et al., 2011).

3 Detection of SARS CoV-2 particles by TLR

One of the most influential families that induce the innate immune system is TLRs (Hemmi et al., 2000). The participation of toll-like receptors in response to coronavirus infection is essential. TLRs participate in the response induced by oxidized phospholipids (OxPLs) that cause the disease by SARS-CoV2. It not only activates the production of type I interferon with the inflammation of cytokines such as IL6 and TNF (tumor necrosis factor), but some other groups of TLRs detect the viral RNA in the endosome (Koon-Guan et al., 2012). TRIF also stimulates the interferon regulatory factor (Uematsu & Akira, 2007). Different pathways associated with TLR signaling can participate in producing cytokines, which convey downstream on the same inflammatory cascade with consequent amplification (Sato et al., 2003). On the other hand, the normalization of adaptor proteins leads to different consequences. The major protein adaptors involved in the TLR pathways in coronavirus infection are TRIF and MyD88 (myeloid differentiation primary response 88). TRIF is linked to TLR3 and chooses the activation of IRF3 and NF- κ B, while MyD-88 interacts with TLR4 and several other proteins, which are involved in IL 1 function, such as IRAK1-2 and interleukin 1 (IL 1) receptor leading to the detection of SARS-CoV-2 infectious particles.

3.1 Toll-like receptors

Toll-like receptors are supposed to be associated with both the initial failure of viral removal and, subsequently, the development of the severe clinical manifestations of the COVID-19, particularly acute respiratory distress syndrome (ARDS) (Onofrio et al., 2020). In humans, there are ten members of the TLRs (*i.e.*, TLR-1-TLR-10), which are expressed in epithelial cells, fibroblasts, and in

different cells of the immune system, including macrophages (Kawasaki & Kawai, 2014). The TLRs can be activated by the various pathogen-associated molecular patterns (PAMPs) present in various species of viruses, bacteria, and other foreign bodies. The activated TLRs play an important role in expressing and releasing several inflammatory mediators, like type-I interferons. Some members of the TLRs (*i.e.*, TLR-1, 2, 4, 5, 6, and 10) are majorly located on the cell surface, while the other members (*i.e.*, TLR-3, 7, 8, and 9) are located on the endosomes. Among these members, TLR-3 identifies the double-stranded RNA, while TLR-7 recognizes the single-stranded viral RNA and hence is involved in the clearance of SARS-CoV-2.

The activation of TLR through TRIF-dependent pathways and MyD88-dependent pathways causes nuclear translocation of the transcription factors, like IRF-3, IRF-7, and NF- κ B, along with the production of type 1 IFN- α/β , and several pro-inflammatory cytokines like IL-1, IL-6, and TNF- α . Analogous to the SARS-CoV, the SARS-CoV-2 may inhibit a successful immune response in the infected individuals and lead to the progression of severe COVID-19, through inhibition of the TNF-receptor associated factors (TRAF-3, and 6), which play an important role in the induction of IRF-3/7 in response to a TLR-7 activation. The currently available agonist against TLR-7 may inhibit the onset of severe COVID-19 in symptomatic patients and can potentiate the effects of anti-viral therapies.

It seems that coronavirus initiates cytokines' release in the body with IL-6 and all the other proteins that activate immune response (Hornung et al., 2009b). The first and foremost defense process in the human body from infections is innate immunity, especially the virus indicating receptor "TLR." Various researches on SARS-CoV-2 represent the participation of TLR-3 in the development of protective effect against coronaviruses (Hornung et al., 2009b). TLRs also recognize PAMPs in the cell membrane, endosomes, lysosomes, and Mitochondrial lysosomes (Hutchens et al., 2008). Incredible TLRs can trigger different organic reactions by activating modified linker proteins such as MyD88, TIR domain-containing adapter protein (TIRAP), excursion, and cable cars (Ermolaeva et al., 2008). MyD88 is the most important relative TIR, used as a linker protein in practically all TLRs except TLR3. It primarily activates NF- κ B translation factors and mitogen-activated protein kinases (MAPK) to initiate the appearance of fiery variables. TLR4 spike protein interaction has shown the strongest protein-protein interaction. Unlike MyD88, TRIF is a TLR3 and TLR4 linker protein that activates IRF3 and NF- κ B translation factors to stimulate the production of interferon type I and inflammatory immune factors. Cable cars and TIRAP are capable of capturing TRIF particles in receptors TLR-4 and MyD88 on TLR2 and TLR4. The TLR pathways, therefore, are transferred to an immuno-inflammatory system dependent on

MyD88 and to a TRIF-based pathway, which can activate interferons and triggers type I. A comparative PAMP initiated; TLR is activated, MyD88 initiates IRAK4, IRAK1, IRAK2, and IRAK-M kinases connected to receptor 1. IRAK4 plays a key role in the NF- κ B and MAPK commissioning under MyD88. IRAK works with TRAF6 that tends to cause its K-63 ubiquitination and encourages ubiquitination to activate NF- κ B. TRIF dependent routes start IRF3 and NF- κ B (Hacker & Karin, 2006), notwithstanding actuating NF- κ B. TRIF-dependent pathways are additionally initiated IRF3 and interferon- β (Häcker et al., 2005). TLRs are PRRs that are restricted to the cell surface or lumen of intracellular vesicles. TLRs are transmembrane type I proteins that consist of three sections. The extracellular part of TLR contains a leucine-rich unit responsible for PAMP recognition, the transmembrane area, and interleukin-1 (IL-1). In mice, thirteen TLRs have been detected, whereas eleven TLRs were found in humans. TLR-1, TLR-2, TLR-4, TLR-5, and TLR-6 are restricted to explicit TLRs' cellular restriction and interpreted as lipids, lipoproteins, and proteins. Intracellular vesicles such as endoplasmic reticulum, endosomes, lysosomes, and endolysosomes are restricted to TLR-3, TLR-7, TLR-8, and TLR-9 (Ewald et al., 2011). Each specific TLR perceives specific pathogenic structures, activates innate reactions, and creates a versatile insensitivity to the antigen. Also, TLR genes display allelic polymorphisms (Menendez et al., 2019) that can affect the strength of the interaction with the relevant ligands or the

subsequent signals transmitted to the nucleus. Monocyte and neutrophils cells are positively associated with TLR-8 with myeloid lineage (Hornung et al., 2009b). The TLR-7 positive plasmacytoid cells are abundantly present in lung tissues (Plantinga et al., 2010). TLR8 is also present in the lungs and recognizes to act on different viruses that cause infection (Heil, 2004). SARS-CoV-2 may induce a cytokine storm (Chiu et al., 2009). The visual illustration of the signaling pathway of the TLRs is shown in figure 1.

In an experimental ARDS mouse model, induced by multiple noxae, having SARS-CoV, the genetic inactivation of the TLR-4 gene, other than TLR-3 or 9 genes, was linked with reduced acute lung injury (Imai et al., 2008). A significant improvement in the levels of IL-6 was also observed, which were comparable with tocilizumab. In patients with severe COVID-19, the lung macrophages play a vital role in the significant release of IL-6 and other cytokines, including IL-10, IL-12, IL-1 β , and TNF- α activations of TLRs (McGonagle et al., 2020). In another study, the stimulation of macrophages with subtype-selective agonists against several TLRs ensured that the stimulation of the TLR-4 induced the strongest effects concerning cytokine release (O'Neill et al., 2013). The SARS-CoV-2 is not likely to directly activate the TLR-4, as the TLR-4 is supposed to be responded by the bacteria. However, based on the mouse model having acute lung injury, one hypothesis is that the oxidized phospholipids are accountable for

Figure 1 Toll-like receptors and TLR signaling pathway

TLR-4 activation and onset of the ARDS (Zuo et al., 2020). It is interesting to note that neutrophil myeloperoxidase, which is reported to be at the highest levels in COVID-19 patients, particularly in those on ventilation aid, possesses the potential to oxidase phospholipids rich in alveolar surfactants (Crouch et al., 2010). Hence, it can be established that TLR-4 may exhibit an efficient target against COVID-19 using TLR-4 antagonists.

A large number of PAMP, such as lipopeptides, peptidoglycan, lipoteichoic acid, are perceived by TLR-2. Heterodimerization shows a specialty for PAMP confirmation. TLR-4 is a significant bacterial marker particle found in the outer membrane of gram-negative microorganisms that recognizes lipopolysaccharides (LPS). TLR-5 detects flagellin, a globular protein present in the most whipped microorganisms, which is the main substituent for bacterial flagella. The TLR-3 and TLR9 recognize dsRNA, polyinosinic-polycytidylic-acid, and unmethylated CpG DNA from bacteria and viruses (Parker et al., 2007). Human TLR-7 and TLR-8 differentiate ssRNA, imidazoquinoline associates, e.g., imiquimod and resiquimod (R-848) and separate guanine analogues. The TLR-9 perceives problems with non-methylated CpG that are typical invertebrate microbial DNA but not genomic DNA. TLRs identify PAMP. PAMP binding with TLRs results in the registration of adapter proteins and the coordination of various signaling pathways leading to different organic reactions (Cao et al., 2019). The linker proteins include myeloid differentiation primary response protein 88 (MyD88), a linker containing-domain-containing adapter-inducing interferon- β (TRIF), also known as TIRAP and TRIF-related linker particles (cable car). TRIF is ingested by TLR-3 and TLR-4, resulting in the activation of IRF3 and NF- κ B and subsequent acceptance of inflammatory cytokines and type I interferon. MyD88 is incredibly easy amongst the TLR connectors. It is a cytosolic protein (DD) disappearance region that is enrolled in active TLRs and has a hexameric structure, leading to higher absorption of DD-containing kinases (Chen et al., 2010). IRAK initiate by phosphorylation; builds a relationship with both an E3 ubiquitin ligase and TRAF6 (a tumor necrosis factor receptor (TNFR)-associated factor 6) collapsing protein. TRAF6 catalyzes the IRAK-1 and TRAF6 self-ubiquitinated K63-linked poly-ubiquitin. Via these ubiquitin-restricting proteins, TRAF6 then binds to the TAK1 (transforming growth factor β (TGF- β) activated protein kinase 1) and TAK1-restricting protein, resulting in IKK complex phosphorylation of the nuclear factor (NF) inhibitor. So, NF- κ B is released for translocation to the nucleus to initiate translation of the explosion's properties. TLRs' stimulation is positively linked with cytokine signaling (Ling et al., 2020). The long sequence of research represents that blocking of TLR signaling avoids the cytokine storms, which symbolize the potential of therapeutic benefits for SARS-CoV-2 that cause initiation of inflammation. Fascinatingly, women were less infected with SARS-CoV-2 infection than men due to their

differences in the immune response, which is the part of innate immunity. TLR7 stimulates the production of interferon, which is present more in women than in men (Liu et al., 2014).

The major hindrance in identifying effective therapies against severe COVID-19 lies in the heterogeneity of the disease and its erratic course, with some patients having mild symptoms exhibiting sudden respiratory failure. On the 1st of May, remdesivir was authorized by the FDA for the treatment of patients having severe COVID-19 requiring hospitalization. Based on the data collected from the NIAID and Gilead sponsored trials, it was found that remdesivir may potentiate the effects of pharmacological agonists against TLR-17, which is supposed to be associated with the mechanism of viral escape from the immune system (Amirian & Levy, 2020). In one study, the TLR-7 agonist administration, i.e., vesatolimod, in simian-human immunodeficient virus (SHIVE-DF162-P3)-infected rhesus monkeys, was associated with a delayed viral rebound after anti-retroviral therapy (Borducchi et al., 2018). In another phase II trial in patients with hepatitis B, the administration of vesatolimod exhibited excellent safety combined with active-anti-viral therapy. The vesatolimod is expected to be safe and biologically active and tested in COVID-19 in combination with other therapies (Janssen et al., 2018). On the other hand, the TLR-4 antagonists can be useful in patients having respiratory support with ARDS, possibly along with anti-IL-6 agents (Opal et al., 2013). A list of Toll-Like receptors and ligands with unique functions is given in Table 1.

3.2 RIG receptors

RIG-I-like receptors (RLR), among their relatives and RIG- (DDX58), MDA5, and LGP2, generally detect the RNA virus from nucleic acids (Lu et al., 2011). The 100-terminal helicase RNA is believed to recognize the structure of CTD and requires a change in the form of ATP associated with the structure of the Mavs cards (Søren Jensen & Thomsen, 2012). RIG-RNA contamination started with a series of infections such as influenza infection, new castle disease virus (NDV), Sendai infection, vesicular stomatitis infection, measles infection, and hepatitis (HCV) (Hemmi et al., 2000). The basic structure is a small, short, and closed double triphosphate with a reciprocal arrangement and rich in poly-UC for viral RNAs. TRS proteins for men and the ADAM receptor for the nucleocapsid receptor contains 5 triphosphate RNA and can be recognized by RIG-end (Akira et al., 2006), and double platform can detect 5'-2' abnormal bases (Chen et al., 2010). An ATP-dependent conformational change perceives the 5'-terminal viral triphosphate ends of the CTD structure. It causes the entire CTD structure to form a double-stranded structure (Cao et al., 2019b). MDA5 detects a picornavirus RNA, including any poliovirus (PV) infection and encephalomyocarditis (EMCV).

Table 1 List of Toll-Likereceptors and their ligands with unique functions

TLRS	Adjuvants	Functions	References
TLR1	Lipopeptides	Cell motility and many others	(Nilsen et al., 2015)
TLR2	Lipoproteins, etc.	Transport mostly fat molecule	(Nilsen et al., 2015)
TLR3	Double-Stranded DNA (dsDNA)	Carry genetic information	(Hornung et al., 2009a)
TLR4	Lipopolysaccharides	Helps in production and structure integrity of cell	(Tang et al., 2016)
TLR5	Flagellin	Gives structure to the cell	(Li et al., 2013)
TLR6	Lipoteichoic acids and other acids	Modify backbone structures present in cells	(Johnsen et al., 2006)
TLR7	Viral RNA	Carry and store cell information	(Johnsen et al., 2006)
TLR8	Viral RNA	Helps in structure formation	(T. Wang et al., 2020)
TLR9	Unmethylated DNA having Cp-G	Activate innate immunity	(Michifumi Yamashita et al., 2012)
TLR10	Not known	Not known but helps to activate innate immunity	(Michifumi Yamashita et al., 2012)
TLR11	Profilin	Helps in polymerization dynamics	(Chen et al., 2010)

3.3 Nucleotide-binding oligomerization domain-like receptors and C-type lectin receptors

Nucleotide-binding oligomerization domain-like receptors (NLRs) are a diverse class of intracellular proteins that display a unique role in host defense and detect PAMPs from invasive pathogens. These receptors are associated with multifunctional roles in innate immunity-related signaling, such as the stimulation of MAPKs, NF- κ B, and inducing cell death following DAMPs or PAMPs response (Koon-Guan et al., 2012). C-type lectin receptors are a large group of transmembrane receptors, which relate to myeloid cells. There are two basic modalities of the effect of CLR implementation on the receptor in cells. Many CLRs efficiently interact with viruses and thus play a pivotal contribution to eradicate viral infections. Nevertheless, it has been revealed that deadly virus particles can subvert CLRs functionalities to escape antiviral immunity and magnify infection. By targeting CLRs, viruses particularly modulate or suppress type I interferons, which in turn exerts a major role in the adaptive and innate defense against viruses (Strasser et al., 2012).

4 Type I interferon

If any virus particle enters the host, the PRRs first sense the viral nucleic, obtain an IRF3 or IRF7 connection and develop the interferon type 1 (IFN). Therefore, type IFNs activate the JAK-STAT downstream signal pathway, promoting IFN-stimulated functionality (ISG) flow (Hara et al., 2013). As the host's main antiviral particles, IFNs also restrict infection and assume an immune-modulatory role to facilitate antibiotic macrophage phagocytosis. Preventing the creation of IFNs in such cases

directly affects the persistence of the host (Strasser et al., 2012). To date, three kinds of IFN producing PRRs are isolated, including TLRs, RLRs, and NLRs (Hemmi et al., 2000). TLR7/TLR9 is perceived to initiate the action of fiery cytokine, type I interferons (IFNs) interceding with NF- κ B, IRF7, and Indiana vesiculovirus (VSV) disease, to initiate miRNA macrophage articulation through RIG or NF- κ B-dependent pathway (Chiu et al., 2009). These infections remain deeply pathogenic, even though SARS-CoV-2 and various coronaviruses are delicate to IFN- α/β . SARS-CoV's 'N' protein acts as a rival of resistant protein from departure and interferon response from the host (Ma & Suthar, 2015). The enterovirus 71 neurological disease (EV71) is responsible for decreasing JAK1, p-JAK1s, and p-TYK2s and restricting the JAK-STAT flagging pathway by IFNs, thereby enhancing IFN ability and promoting replication and proliferation of EV71s in cells has been removed (Ivashkiv & Donlin, 2013). EBOV (Ebola virus infection) activates the suppressor of cytokine signalling-1 (SOCS1) gene, which inhibits by specifically activating phosphorylated JAK, and impairing its function JAK-STAT (Cao et al., 2019a). Also, in the flu virus, the downstream pathway of IFN- α can be inhibited by the infection, by stimulating the expression of SOCS3 (Jensen & Thomsen, 2012).

5 Immune response of T cells

The MERS-CoV and SARS-CoV are β -coronavirus that cause life-threatening diseases in the respiratory system (Hornung et al., 2009a). Lymphocytes, CD4+leukocytes, and particularly CD8+leukocytes do enormous antiviral work by regulating pathogens and overcoming autoimmunity risk (Sun et al., 2012). CD4 + lymphocytes cause T-dependent B cells to stimulate the

development of virus-specific antibodies. Nevertheless, the CD8+ immune system's microorganisms are cytotoxic and may destroy infected virus cells. In patients with SARS-CoV disease, CD8+ leukocytes represent roughly 80% of every single incendiary cell that enters the interstitial lung and assume an essential role in expelling CoV from defiled cells inciting innocuous injuries (Nelemans & Kikkert, 2019). It emphasized the critical role of lymphocytes on B cells in controlling the pathogenesis of MERS-CoV infection. The cross-reaction of microorganisms in the immune system leads to a decrease in MERS-CoV. However, CD4+ leukocytes have no defense against MERS-CoV disease. During SARS-CoV contamination, depletion of CD8+ leukocytes will not affect and delay virus replication (Baccala et al., 2009). CD4+ leukocyte depletion is associated with lymphopenia, immunization death, and cytokine production, leading to solid immunity-mediated interstitial pneumonia and SARS-CoV margin delay in the lungs (Phadwal et al., 2012).

Furthermore, T cells also generate pro-inflammatory cytokines through the NF- κ B signaling pathway (Schneider et al., 2014). Cytokine IL-17 can aggravate monocytes and neutrophils at the site of the disease and activate some downstream chemokines and cytokines, such as "IL-1, LL-6, IL-8, IL-21, TNF- β , and MCP-1" (Spiegel et al., 2005). Similarly, MERS-CoV induces apoptosis of lymphocytes by initiating innate and extrinsic apoptotic pathways. SARS-CoV-specific leukocytes were screened to gain strength in SARS patients (Groskreutz et al., 2006). All the identified leukocytes respond directly to the SARS-CoV accessory protein. The two responses of CD8+ T lymphocytes to SARS-CoV and nucleocapsid (N) membrane proteins are described by estimating their HLA limitation and negligible epitope regions of immune microorganisms. These reactions are expected to last up to 11 years after becoming ill (Aeffner et al., 2011). Similarly, it was demonstrated that these responses of CD8+ T lymphocytes to MERS-CoV lack cross-reactivity. The reaction of white blood cells with protein S and other basic proteins (counting protein M and N) is long-lasting and tireless. This provides evidence of the SARS vaccination plan for the virus' basic protein, which can trigger a major, convincing, and long-term response of memory cells against the virus (Lu et al., 2010).

6 Antibody response to coronaviruses infection

Dynamic reactions in *in-vivo* neutralizer and glycoprotein infection envelop need modifications with viral anticorporate to diversify antigenic goals. It is necessary to determine whether antibodies are unexpected in CoV's incomprehensible multiple infections like MERS (Hutchens et al., 2007). Work from all over the world has shown over 20 kinds of monoclonal antibodies, mainly human or adapted antibodies. The infection uses the spike protein as a grip factor, promoting a dipeptidyl peptidase-4 (DPP4) section (Kuba et al., 2005). In infected patients with acquired and innate resistance,

this receptor is a crucial factor in the transmission and action of symptoms. Consequently, the technique of monoclonal antibodies against these proteins has a special defensive effect, as contrasted and as time-consuming as immunization (Ewald et al., 2011). A monoclonal counter acting agent (m336) of a person, separated from the phage display library, interacts with a MERS coronavirus spike protein receptor-binding region, showing stable balance mobility in MERS-CoV in *in-vitro*. The *in-vitro* MERS-CoV demonstrates the right balance of the human monoclonal neutralizer m336. The titer of lung RNA grows from 40000 to 90000 fold per m336 (Liu et al., 2014). The disease after MERS-CoV was treated with hyperimmune plasma with chat titer or granular immunization m336. Two collections carry weak indications of clinical disease, decreased respiratory viral load; however, it is the only collection of hyperimmune plasma.

Despite the disposition of each of these modalities of the disease, the treatment could not be too wounded, and the base of m336 counts that they must exhibit (Kopecky-Bromberg et al., 2006). However, as HMAb m336 has weakened, and viral RNA becomes neurotic, the viruses associated with the changes need to be vaccinated. No protective antibodies in the mice had lung tissue against heterovirus (Seranova et al., 2019). Following the reinforcement of SAR-SCoV, inoculated ferrets produced a quick and more grounded immunizing response than the control creatures; however, the liver's robust flaming response was seen. In this case, SARS-CoV S is associated with increased hepatitis (Liu et al., 2014). And again, the course of the SARS-CoV viremia and the acting agent is growing. There is no way to recover blood tests in patients. The pinnacle of time, viremia, 75% of patients were exposed to SARS through a first blood test, in the previous four days, it was discovered that they did not recognize ribosomal RNA (Garcia-Cattaneo et al., 2012). The extended production of IgG could prove that it is both a comfortable and safe reaction to the intensive contamination of SARS-CoV and a free retrieval of the rest of the sources of infection. *Clostridium perfringens*, in any case extending the creature's importance entirely in order not to worry about SARS. Let it show, using the principles of regaining the freedom of contamination of the rest. This was obsessed with more significant work (Chan et al., 2015).

7 TLR3 pathway

TLR3 is located in a network of unstimulated cells, and the incentive traffic of ssDNA indicates that the pH of the subordinate component of the vocational ligand of the endosomes also requires the dimerization of TLR3 (Gattinon & Carlesso, 2018). The communication between the UNC93B1 gene protein, which is essential for the endoplasmic reticulum and the TLR3 dealing and signaling, has been amply demonstrated, the duration of the necessary tests works on the basic structure of TLR3. The dsRNA recognizes it and the amount of signaling. Increasing evidence

suggests that cathepsin and asparagine proteolysis of the TLR nebulin from endolysosomes speak to the general administration procedure of all TLRs associated with corrosive nucleic recognition (Wang et al., 2020). TLR3 proteolytic management manages endosomal safety and limitation. However, it is still an excellent job on their well understood TLR3. Additional TLR3 tyrosine phosphorylation in endosomes is the enrollment of husky linking the interleukin-1 protein, connecting the interferon- β (IFN- β) protein a TIR-TLR3 area. This is different from endosomal TLRs (TLR7-9) in requiring that there is no tyrosine phosphorylation because MyD88 is a subordinate with no initials (Seranova et al., 2019). TLR3 is good to be recognized and optimized for visiting renewed phosphorylate battles (Souyris et al., 2018). Two studies have written difficult work for the iron tyrosine kinase Src13, epidural factor, and mal 14 receptor in phosphorylation of the TLR3 development center. These tests confirm that the model is now inciting harmful ssDNA and connects TLR3 acute development.

Interestingly, Tyr759 phosphorylation would involve the production of the epidermalib needed for the phosphorylation of Src factor Tyr858. Additionally, the 3-tyrosine enzyme phosphoinositide, the Bruton enzyme, and the TLR3 phosphorylation were identified. Phosphoinositide 3 kinase is necessary for the complete interpretation of an administrative element IFN γ (IRF3) and nuclear factor κ B (NF- κ B), but its office with TLR3 ensures that it will stop. Bruton tyrosine kinase phosphorylates helps in the accumulation of Tyr759 by TLR3 (Channappanavar et al., 2014). Bruton's tyrosine enzyme has large phages; 3- β phosphoinositide, AKT, and mitogenic cavity with protein (MAPK) started by TLR3 and the promulgation of NF- κ B. Two-phase dimerization and activation of TLR3, by phosphorylation of the impact of the translation of the IRF3 factors NF- κ B-1 and two-armed AP.

Class NF- κ B and AP-1, on a protein associated with the receptor-interacting protein 1 (RIP1) and E3 ubiquitin-protein ligase TRAF6, and connected to TRIF and selected tab2 (term TAK1 protein 2), tab3 (term TAK1 protein 3) and TAK1 (change- β and evolve to act on the zoom-I factor). This implements this type and all IKK (fundamental modulating modular factor- κ B, Ikka, IKK β), MAPK along the way, and an additional act of NF and AP-1 each. Receptor-interacting protein 1 (RIP1) brings here, and in whose branches, TRAF3 gives the greatness to begin the reaction to the burning antiviral material, which show act on another type of IFN I cytokine. It is interesting to note that the TRIF-RIP1 connection; rejects the cell death by the protein bound to the Fas/caspase-8-virion space belongs and the pathway. Undoubtedly, TLR3, TRIF pivot has cytopathic potential, which can be created in infection (Cao et al., 2019). It was evident that by prohibiting these data suggests that TLR3 can expect three significant results: (1) the action of an animal

of such progress IRF3 is opening the road; (2) a cytopathic passage through the cell of the impact syndrome or RIP1 activation in 8 phases; (3) there was an inflammatory condition of initiation of NF- κ B and AP-1 (Wang et al., 2014).

8 Viral respiratory infections

Rhinovirus, influenza-A infections, and respiratory syncytial infections have been tested for the presence of TLR3 in respiratory virus exposure. Rhinovirus is the most common cause of asthma and can be concentrated in *in-vivo* using rhinovirus type 1 strain (RV-1), a mild aggregation infection replicated in mice's lungs (Johnsen et al., 2006). Mice without TLR3 reported a decrease in inflamed lung responses and decreased airway reactivity, suggesting that rhinovirus infection has significant authority for viral dsRNA. TLR3 opens up inflammatory signaling pathways that worsen the route and hyperreactivity (Yamashita et al., 2012). By comparison, IAV-contaminated mice without TLR3 had increased endurance rates even though the lungs' viral weight was high, which was reduced entirely. Additionally, respiratory syncytial infection infects the respiratory tract's epithelial cells explicitly and causes these diseases of the upper respiratory tract, intensification of asthma, and pneumonia. The respiratory syncytial infection starts up TLR3, preparing lung epithelial cells to introduce further extracellular dsRNA (Sato et al., 2003a). When TLR3 is induced, the proliferation of NF- κ B and prolonged IL-8 levels increases the epithelial cells' reactivity, which leads to a modified inflammatory response (Lee et al., 2012). Aeffner and coworkers reported that dsRNA trigger lungs function comparable to a respiratory syncytial infectious disease in mice. Mice without TLR3 had significantly less viral replication in the respiratory tract and less spread of the infection to the gastric organs (Pauli et al., 2008a). Mice without TLR3 had reduced morbidity and lung irritation leading to decreased lung uptake of leukocytes. Also, mice without TLR3 had lower levels of fiery cytokines, including serum IL-6, serum monocyte protein 1, TNF, or even bronchoalveolar fluid lavage (Kim et al., 2008). IFN- β levels did not correlate with the mouse (Okumura et al., 2009). Taken together, these results show that TLR3 may have an adverse effect in the airways, which promotes a possible over-triggering of the ace provocation response on flight routes that are unfavorable for the host (Cecere et al., 2012; Chan et al., 2015).

9 Methodology

We searched MEDLINE using PubMed, Embase, Web of Science, China National Information Foundation (CNKI), Wanfang Information, and China Science Medication (CBM) with the expressions "COVID-19", "SARS-CoV-2", "2019 novel coronavirus", "2019-nCoV", "Wuhan coronavirus", "novel coronavirus", "Wuhan pneumonia infection", or "Wuhan infection". We additionally looked through Google Researcher; the official sites

of WHO (<https://www.who.int/>), US CDC (<https://www.cdc.gov/>), ECDC (<https://www.ecdc.europa.eu/en/>), General Wellbeing Britain (PHE) (<https://www.gov.uk/government/associations/general-wellbeing-britain>); some preprint servers, including BioRxiv (<https://www.biorxiv.org/>), ChemRxiv (<https://chemrxiv.org/>), medRxiv (<https://www.medrxiv.org/>) and SSRN (<https://www.ssrn.com/index.cfm/en/>); and reference arrangements of the distinguished articles to discover reports of extra examinations. We incorporated all writing identified with COVID-19 distributed in English and Chinese from the beginning of the pandemic till now without limitations, including direction/rules, surveys, clinical investigations, essential research, epidemiological examinations, and remarks. Reports and direction/rules posted by universal associations, government establishments, affiliations, and social orders were likewise included. We avoided news reports that were not distributed in logical diaries and articles where we neglected to get to full content despite reaching the writers.

Conclusions

We concluded that the pandemic starts in China and is known as COVID-19, which infected the whole world. According to recent studies, more than 7 million people are infected worldwide. Till now, the worldwide population is also infected. Many receptors are included in this infection. While the research of TLR3 on viral contamination protection may be shifting among infections, TLR3's impeding commitment to viral pathogenesis has emerged from mouse and human viral studies. TLR3 is concerned with defending and offending against infection resistance. A working model of TLR3 function, based on the writing, on antiviral (defensive) and immuno-regulatory (inhibiting) reactions. We have a lot to find out about the instruments that drive TLR3-intervened ailment regarding viral diseases and, critically, in autoimmunity and malignancies that happen after specific contaminations.

Toll-like receptors 3 (TLR3) has resistance to infection both in barrier and attack. TLR3 perceives dsRNA, which is typical for multiple infections of replication. TLR3 may also have a major pathogenic impact in some common contaminations in the modification guideline for lymphocyte polarization. Virally infected cells develop flags to help cross-preparation on dendritic cells (DCs). Type I IFN emission, known to enhance cross-introduction by DCs and interfere in antiviral insusceptibility against several viral infections, is enabled on dsRNA acknowledgment. These occasion outcomes the activation in Th1 reactions and cytotoxic T lymphocyte. The useful or inconvenient job of TLR3 adjusting the response towards Th1 resistance upon tissue-explicit viral diseases would extraordinarily wander contingent upon the capacity. The cell conditions to adjust by creating the Th2 partner reaction. Additionally, a solitary viral pathogen routinely characterized as Th1-incident bears an assortment of ligands equipped for drawing in various TLRs that can likewise invigorate a Th2 response, even

though to an alternate degree. Along these lines, a superior comprehension of the Th1 and Th2 reaction regulation through TLR3 incitement in infection driven tissue-explicit pathogenesis is fundamental. Regarding ceaseless RNA viral contaminations that bring about continued IFN- α/β motioning, without viral control, the TLR3–TRIF pivot may assume significant jobs in deciding how the harmony among antiviral and immune-regulatory pathways influence defensive versus inconvenient reactions.

It will be essential to decide if TLR3 has a non-recurring and protective role with viral conditions other than herpes simplex encephalitis. A present aim is to grasp this extraordinary and perhaps fascinating mission in full. Another exciting task is to recognize subordinate, TRIF autonomous ways and obligations to TLR3 during illness, autoimmunity, and malignancy. In its earliest stages, and any case, in liver97 and kidney99, enactment TLL 3 can lead separately to hepatitis and glomerulonephritis of the immune system, we understand the possible differential jobs of TLR3 for certain organs. For instance, poly(I: C) is evaluated to boost anti-function. How can a restorative TLR3 in specific individuals, depending on the nature of TLR3's disadvantageous role in specific diseases, exasperate pathogenesis for antiviral usage? It is most likely that special restorative strategies are built to reduce TLR3-driven infections later.

Acknowledgment

All the listed author(s) are thankful to their representative universities/institutes for providing the related support to compile this work.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Aeffner F, Traylor ZP, Yu ENZ, Davis IC (2011) Double-stranded RNA induces similar pulmonary dysfunction to respiratory syncytial virus in BALB/c mice. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 301(1): 99-109.
- Akira S, Uematsu S, Takeuchi O (2006) Pathogen Recognition and Innate Immunity. *Cell* 124(4): 783–801.
- Amirian ES, Levy JK (2020) Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. *One Health* 9: 100128.
- Baccala R, Gonzalez-Quintial R, Lawson BR, Stern ME, Kono DH, Beutler B, Theofilopoulos A N (2009) Sensors of the innate immune system: their mode of action. *Nature Reviews Rheumatology* 5(8): 448–456.

- Bilal M, Khan MI, Nazir MS, Ahmed I, Iqbal HMN (2020a) Coronaviruses and COVID-19 – Complications and Lessons Learned for the Future. *Journal of Pure and Applied Microbiology* 14(suppl 1): 725-731.
- Bilal M, Nazir MS, Parra-Saldivar R, Iqbal HM (2020b) 2019-NCOV/COVID-19-Approaches to viral vaccine development and preventive measures. *Journal of Pure and Applied Microbiology*, 14(1): 25-29.
- Borducchi EN, Li J, Nkolola JP, Cadena AM, Yu WH, Fischinger S, Barouch DH (2018) Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys. *Nature* 563(7731): 360–364.
- Cao L, Ji Y, Zeng L, Liu Q, Zhang Z, Guo S, Guo D (2019a) P200 family protein IFI 204 negatively regulates type I interferon responses by targeting IRF7 in nucleus. *PLOS Pathogens* 15(10): 1008079.
- Cao L, Ji Y, Zeng L, Liu Q, Zhang Z, Guo S, Guo D (2019b) P200 family protein IFI204 negatively regulates type I interferon responses by targeting IRF7 in nucleus. *PLoS Pathogens* 15(10): 1008079.
- Cecere TE, Todd SM, LeRoith T (2012) Regulatory T Cells in Arterivirus and Coronavirus Infections: Do They Protect Against Disease or Enhance it? *Viruses* 4(5): 833–846.
- Chan JFW, Lau SKP, To KKW, Cheng VCC, Woo PCY, Yuen KY (2015) Middle East Respiratory Syndrome Coronavirus: Another Zoonotic Betacoronavirus Causing SARS-Like Disease. *Clinical Microbiology Reviews* 28(2): 465–522.
- Channappanavar R, Fett C, Zhao J, Meyerholz DK, Perlman S (2014) Virus-Specific Memory CD8 T Cells Provide Substantial Protection from Lethal Severe Acute Respiratory Syndrome Coronavirus Infection. *Journal of Virology* 88(19): 11034–11044.
- Chen J, Lau YF, Lamirande EW, Paddock C D, Bartlett JH, Zaki SR, Subbarao K (2010) Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. *Journal of Virology* 84(3): 1289–1301.
- Chiu YH, Macmillan JB, Chen ZJ (2009) RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. *Cell* 138(3): 576–591.
- Chiu YH, MacMillan JB, Chen ZJ (2009) RNA Polymerase III Detects Cytosolic DNA and Induces Type I Interferons through the RIG-I Pathway. *Cell* 138(3): 576–591.
- Crouch EC, Hirche TO, Shao B, Boxio R, Wartelle J, Benabid R, Belaouaj A (2010) Myeloperoxidase-dependent inactivation of surfactant protein D in vitro and in vivo. *The Journal of Biological Chemistry* 285(22): 16757–16770.
- Dhama K, Sharun K, Tiwari R, Sircar S, Bhat S, Malik YS, Rodriguez-Morales AJ (2020) Coronavirus Disease 2019 & ndash COVID-19, <https://doi.org/10.20944/preprints202003.0001.v2>.
- Ermolaeva MA, Michallet MC, Papadopoulos N, Utermöhlen O, Kranidioti K, Kollias G, Pasparakis M (2008) Function of TRADD in tumor necrosis factor receptor 1 signaling and in TRIF-dependent inflammatory responses. *Nature Immunology* 9(9): 1037–1046.
- Ewald SE, Engel A, Lee J, Wang M, Bogoy M, Barton GM (2011) Nucleic acid recognition by Toll-like receptors is coupled to stepwise processing by cathepsins and asparagine endopeptidase. *The Journal of Experimental Medicine* 208(4): 643–651.
- Garcia-Cattaneo A, Gobert FX, Muller M, Toscano F, Flores M, Lescure A, Benaroch P (2012) Cleavage of Toll-like receptor 3 by cathepsins B and H is essential for signaling. *Proceedings of the National Academy of Sciences* 109(23): 9053–9058.
- Garcia-Cattaneo FX, Müller M, Toscano F, Flores M, Lescure A, Benaroch P (2012) Cleavage of Toll-like receptor 3 by cathepsins B and H is essential for signaling. *Proceedings of the National Academy of Sciences of the United States of America* 109(23): 9053–9058.
- Gattinoni L, Carlesso E (2018) Acute respiratory failure and acute respiratory distress syndrome, https://doi.org/10.1093/med/9780199687039.003.0064_update_001
- Groskreutz DJ, Monick MM, Powers LS, Yarovsky TO, Look DC, Hunninghake GW (2006) Respiratory Syncytial Virus Induces TLR3 Protein and Protein Kinase R, Leading to Increased Double-Stranded RNA Responsiveness in Airway Epithelial Cells. *The Journal of Immunology* 176(3): 1733–1740.
- Group TWH (2013) State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. *PLoS Currents* <https://doi.org/10.1371/currents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8>.
- Hacker H, Karin M (2006) Regulation and Function of IKK and IKK-Related Kinases. *Science* 311(5761): 19–22.
- Häcker H, Redecke V, Blagoev B, Kratchmarova I, Hsu LC, Wang GG, Karin M (2005) Specificity in Toll-like receptor signalling through distinct effector functions of TRAF3 and TRAF6. *Nature* 439(7073): 204–207.
- Hara H, Tsuchiya K, Kawamura I, Fang R, Hernandez-Cuellar E, Shen Y, Mitsuyama M (2013) Phosphorylation of the adaptor ASC acts as a molecular switch that controls the formation of speck-like

- aggregates and inflammasome activity. *Nature Immunology* 14(12): 1247–1255.
- Heil F (2004) Species-Specific Recognition of Single-Stranded RNA via Toll-like Receptor 7 and 8. *Science* 303(5663): 1526–1529.
- Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Akira S (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* 408(6813): 740–745.
- Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Fitzgerald KA (2009a) AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* 458(7237): 514–518.
- Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Fitzgerald KA (2009b) AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* 458(7237): 514–518.
- Hughes K (2013) A global collaborative approach to human health risk assessment: The {WHO} chemical risk assessment network. *Toxicology Letters* 221: 212.
- Hutchens M, Luker KE, Sottile P, Sonstein J, Lukacs NW, Núñez G, Luker GD (2007) TLR3 Increases Disease Morbidity and Mortality from Vaccinia Infection. *The Journal of Immunology* 180(1): 483–491.
- Hutchens M, Luker KE, Sottile P, Sonstein J, Lukacs NW, Núñez G, Luker GD (2008) TLR3 increases disease morbidity and mortality from vaccinia infection. *Journal of Immunology* 180(1): 483–491.
- Iqbal, HM, Romero-Castillo KD, Bilal M, Parra-Saldivar R (2020) The emergence of novel-coronavirus and its replication cycle: an overview. *Journal of Pure and Applied Microbiology* 14(1):13-16.
- Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Penninger JM (2008) Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell* 133(2): 235–249.
- Ivashkiv LB, Donlin LT (2013) Regulation of type I interferon responses. *Nature Reviews Immunology* 14(1): 36–49.
- Janssen HLA, Brunetto MR, Kim YJ, Ferrari C, Massetto B, Nguyen AH, Gane EJ (2018) Safety, efficacy and pharmacodynamics of vesatolimod (GS-9620) in virally suppressed patients with chronic hepatitis B. *Journal of Hepatology* 68(3): 431–440.
- Jensen S, Thomsen AR (2012) Sensing of RNA Viruses: a Review of Innate Immune Receptors Involved in Recognizing RNA Virus Invasion. *Journal of Virology* 86(6): 2900–2910.
- Jensen Søren, Thomsen AR (2012) Sensing of RNA viruses: a review of innate immune receptors involved in recognizing RNA virus invasion. *Journal of Virology* 86(6): 2900–2910.
- Johnsen IB, Nguyen TT, Ringdal M, Tryggestad AM, Bakke O, Lien E, Anthonsen MW (2006) Toll-like receptor 3 associates with c-Src tyrosine kinase on endosomes to initiate antiviral signaling. *The EMBO Journal* 25(14): 3335–3346.
- Kawasaki T, Kawai T (2014) Toll-like receptor signaling pathways. *Frontiers in Immunology* 5: 461.
- Kell AM, Gale M (2015) RIG-I in RNA virus recognition. *Virology* 479, 110–121.
- Khanda R, Dadar M, Munjal A, Dhama K, Karthik K, Tiwari R, Chaicumpa W (2019) A Comprehensive Review of Autophagy and Its Various Roles in Infectious, Non-Infectious, and Lifestyle Diseases: Current Knowledge and Prospects for Disease Prevention, Novel Drug Design, and Therapy. *Cells* 8(7): 674.
- Ki M (2020) Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Korea. *Epidemiology and Health* 42: 2020007.
- Kim YM, Brinkmann MM, Paquet ME, Ploegh HL (2008) UNC93B1 delivers nucleotide-sensing toll-like receptors to endolysosomes. *Nature* 452(7184): 234–238.
- Koh D, Sng J (2010) Lessons From the Past: Perspectives on Severe Acute Respiratory Syndrome. *Asia Pacific Journal of Public Health*, 22(3): 132S–136S.
- Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P (2006) Severe Acute Respiratory Syndrome Coronavirus Open Reading Frame (ORF) 3b ORF 6, and Nucleocapsid Proteins Function as Interferon Antagonists. *Journal of Virology* 81(2): 548–557.
- Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Penninger JM (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine* 11(8): 875–879.
- Lee KG, Xu S, Kang ZH, Huo J, Huang M, Liu D, Lam KP (2012) Bruton tyrosine kinase phosphorylates Toll-like receptor 3 to initiate antiviral response. *Proceedings of the National Academy of Sciences* 109(15): 5791–5796.
- Lee Koon-Guan, Xu S, Kang ZH, Huo J, Huang M, Liu D, Lam KP (2012) Bruton's tyrosine kinase phosphorylates Toll-like

- receptor 3 to initiate antiviral response. *Proceedings of the National Academy of Sciences of the United States of America* 109(15): 5791–5796.
- Li Y, Chen M, Cao H, Zhu Y, Zheng J, Zhou H (2013) Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. *Microbes and Infection* 15(2): 88–95.
- Ling L, Lu Y, Zhang Y, Zhu H, TuP, Li H, Chen D (2020) Flavonoids from *Houttuynia cordata* attenuate H1N1-induced acute lung injury in mice via inhibition of influenza virus and Toll-like receptor signalling. *Phytomedicine* 67: 153150.
- Liu Y, Zhang Z, Zhao X, Yu R, Zhang X, Wu S, Chen W (2014) Enterovirus 71 Inhibits Cellular Type I Interferon Signaling by Downregulating JAK1 Protein Expression. *Viral Immunology* 27(6): 267–276.
- Lu X, Pan J, Tao J, Guo D (2010) SARS-CoV nucleocapsid protein antagonizes IFN- γ response by targeting initial step of IFN γ induction pathway, and its C-terminal region is critical for the antagonism. *Virus Genes* 42(1): 37–45.
- Lu X, Pan J, Tao J, Guo D (2011) SARS-CoV nucleocapsid protein antagonizes IFN- β response by targeting initial step of IFN- β induction pathway, and its C-terminal region is critical for the antagonism. *Virus Genes* 42(1): 37–45.
- Ma DY, Suthar MS (2015) Mechanisms of innate immune evasion in re-emerging RNA viruses. *Current Opinion in Virology* 12: 26–37.
- McGonagle D, Sharif K, O'Regan A, Bridgewood C (2020) The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmunity Reviews* 19(6): 102537.
- Menendez D, Snipe J, Marzec J, Innes CL, Polack FP, Caballero MT, Resnick MA (2019) p53-responsive TLR8 SNP enhances human innate immune response to respiratory syncytial virus. *The Journal of Clinical Investigation* 129(11): 4875–4884.
- Nelemans T, Kikkert M (2019) Viral Innate Immune Evasion and the Pathogenesis of Emerging RNA Virus Infections. *Viruses* 11(10): 961.
- Nilsen NJ, Vladimer GI, Stenvik J, Orning MPA, Zeid-Kilani MV, Bugge M, Lien E (2015) A role for the adaptor proteins TRAM and TRIF in toll-like receptor 2 signaling. *The Journal of Biological Chemistry* 290(6): 3209–3222.
- O'Neill LAJ, Golenbock D, Bowie AG (2013). The history of Toll-like receptors — redefining innate immunity. *Nature Reviews Immunology* 13(6): 453–460.
- Okumura A, Pitha PM, Yoshimura A, Harty RN (2009) Interaction between Ebola Virus Glycoprotein and Host Toll-Like Receptor 4 Leads to Induction of Proinflammatory Cytokines and SOCS1. *Journal of Virology* 84(1): 27–33.
- Onofrio L, Caraglia M, Facchini G, Margherita V, Placido S De, Buonerba C (2020) Toll-like receptors and COVID-19: a two-faced story with an exciting ending. *Future Science OA* 6(8): 605.
- Opal SM, Laterre PF, Francois B, LaRosa SP, Angus DC, Mira JP (2013) Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis. *JAMA*, 309(11):1154.
- Parker LC, Prince LR, Sabroe I (2007) Translational mini-review series on Toll-like receptors: networks regulated by Toll-like receptors mediate innate and adaptive immunity. *Clinical and Experimental Immunology* 147(2): 199–207.
- Pauli EK, Schmolke M, Wolff T, Viemann D, Roth J, Bode JG, Ludwig S (2008a) Influenza A Virus Inhibits Type I IFN Signaling via NF- κ B-Dependent Induction of SOCS-3 Expression. *PLoS Pathogens* 4(11): e1000196.
- Pauli EK, Schmolke M, Wolff T, Viemann D, Roth J, Bode JG, Ludwig S (2008b) Influenza A virus inhibits type I IFN signaling via NF- κ B-dependent induction of SOCS-3 expression. *PLoS Pathogens* 4(11): e1000196.
- Phadwal K, Alegre-Abarrategui J, Watson AS, Pike L, Anbalagan S, Hammond EM, Simon AK (2012) A novel method for autophagy detection in primary cells. *Autophagy* 8(4): 677–689.
- Plantinga M, Hammad H, Lambrecht BN (2010) Origin and functional specializations of DC subsets in the lung. *European Journal of Immunology* 40(8): 2112–2118.
- Sato S, Sugiyama M, Yamamoto M, Watanabe Y, Kawai T, Takeda K, Akira S (2003a) Toll/IL-1 Receptor Domain-Containing Adaptor Inducing IFN- γ (TRIF) Associates with TNF Receptor-Associated Factor 6 and TANK-Binding Kinase 1, and Activates Two Distinct Transcription Factors, NF- κ B and IFN-Regulatory Factor-3, in the Toll-Like Receptor Signaling. *The Journal of Immunology* 171(8): 4304–4310.
- Sato S, Sugiyama M, Yamamoto M, Watanabe Y, Kawai T, Takeda K, Akira S (2003b) Toll/IL-1 Receptor Domain-Containing Adaptor Inducing IFN- β (TRIF) Associates with TNF Receptor-Associated Factor 6 and TANK-Binding Kinase 1, and Activates Two Distinct Transcription Factors, NF- κ B and IFN-Regulatory Factor-3, in the Toll-Like Receptor S. *The Journal of*

- Immunology 171(8): 4304–4310.
- Schneider WM, Chevillotte MD, Rice CM (2014) Interferon-Stimulated Genes: A Complex Web of Host Defenses. *Annual Review of Immunology* 32(1): 513–545.
- Seranova E, Ward C, Chipara M, Rosenstock TR, Sarkar S (2019) In Vitro Screening Platforms for Identifying Autophagy Modulators in Mammalian Cells. In *Methods in Molecular Biology* 1880:389–428. DOI: https://doi.org/10.1007/978-1-4939-8873-0_26
- Shah STA, Mansoor M, Mirza AF, Dilshad M, Khan MI, Farwa R, Khan MA, Bilal M, Iqbal HMN (2020) Predicting COVID-19 Spread in Pakistan using the SIR Model. *Journal of Pure and Applied Microbiology* 14(2): 1423–1430.
- Souyris M, Cenac C, Azar P, Daviaud D, Canivet A, Grunewald S, Guéry JC (2018) TLR7 escapes X chromosome inactivation in immune cells. *Science Immunology* 3(19): 8855.
- Spiegel M, Pichlmair A, Martinez-Sobrido L, Cros J, Garcí'a-Sastre A, Haller O, Weber F (2005) Inhibition of Beta Interferon Induction by Severe Acute Respiratory Syndrome Coronavirus Suggests a Two-Step Model for Activation of Interferon Regulatory Factor 3. *Journal of Virology* 79(4): 2079–2086.
- Strasser D, Neumann K, Bergmann H, Marakalala M, Guler R, Rojowska A, Ruland J (2012) Syk Kinase-Coupled C-type Lectin Receptors Engage Protein Kinase C- δ to Elicit Card9 Adaptor-Mediated Innate Immunity. *Immunity* 36(1): 32–42.
- Sun L, Wu J, Du F, Chen X, Chen ZJ (2012) Cyclic GMP-AMP Synthase Is a Cytosolic DNA Sensor That Activates the Type I Interferon Pathway. *Science* 339(6121): 786–791.
- Tang FSM, Van Ly D, Spann K, Reading PC, Burgess JK, Hartl D, Oliver BG (2016) Differential neutrophil activation in viral infections: Enhanced TLR-7/8-mediated CXCL8 release in asthma. *Respirology* 21(1): 172–179.
- Uematsu S, Akira S (2007) Toll-like Receptors and Type I Interferons. *Journal of Biological Chemistry* 282(21): 15319–15323.
- Wang CM, Chang SW, Wu YJ, Lin JC, Ho HH, Chou TC, Chen JY (2014) Genetic variations in Toll-like receptors (TLRs 3/7/8) are associated with systemic lupus erythematosus in a Taiwanese population. *Scientific Reports* 4: 3792.
- Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B (2020). Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet* 395(10228): 52.
- Yamashita M, Chattopadhyay S, Fensterl V, Saikia P, Wetzel JL, Sen GC (2012) Epidermal Growth Factor Receptor Is Essential for Toll-Like Receptor 3 Signaling. *Science Signaling* 5(233): 50.
- Yamashita M, Chattopadhyay S, Fensterl V, Saikia P, Wetzel JL, Sen GC (2012) Epidermal growth factor receptor is essential for Toll-like receptor 3 signaling. *Science Signaling* 5(233): 50.
- Zhao J, Li K, Wohlford-Lenane C, Agnihothram SS, Fett C, Zhao J, Perlman S (2014) Rapid generation of a mouse model for Middle East respiratory syndrome. *Proceedings of the National Academy of Sciences* 111(13): 4970–4975.
- Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, Knight JS (2020) Neutrophil extracellular traps (NETs) as markers of disease severity in COVID-19. *MedRxiv: The Preprint Server for Health Sciences*, <https://doi.org/10.1101/2020.04.09.20059626>