SARS-CoV-2 Receptors

Subjects: Virology

Contributor: Filopateer Nasser

Different host-cell receptors are utilized by viral proteins to recognize host cells, such as integrins, angiotensin-converting enzyme 2 (ACE2), sialic acid receptors, dipeptidyl peptidase 4 (DPP4), and glucose regulated protein 78 (GRP78).

Keywords: human coronavirus ; cell receptor ; SARS-CoV-2 ; COVID-19

1. Introduction

Human coronaviruses (CoVs) are a new type of virus (order Nidovirales) identified in the mid-1960s and classified taxonomically under Coronaviridae family and Coronavirinae subfamily [1][2]. Coronaviruses are given this name for the crown-like spikes on their surface and are classified, based on their genetics, into four main groups known as alpha, beta, gamma, and delta coronaviruses. The majority of gamma coronaviruses and delta coronaviruses affect birds, whereas alpha coronaviruses and beta coronaviruses infect rodents and bats [3]. There are seven known coronavirus strains that can infect humans: 229E and NL63—alpha coronaviruses; OC43, HKU1, MERS-CoV, SARS-CoV, and the newly identified SARS-CoV-2—beta coronaviruses [4]. Sometimes coronaviruses that infect animals can also make people sick and turn into human coronaviruses, as in cases with SARS-CoV, MERS-CoV, and the new SARS-CoV-2 [5][6]. The infectious bronchitis virus (IBV) was the first CoV discovered, and it primarily infected the respiratory systems of chickens. On the other hand, the first two human coronaviruses identified were HCoV-229E and HCoV-OC43, which cause common cold symptoms in people [7][8].

Severe acute respiratory syndrome (SARS), which is a viral respiratory disease caused by a SARS-associated coronavirus (SARS-CoV), was first identified in 2003 during an outbreak that emerged in China and then spread to more than 30 countries, resulting in a fatality rate of nearly 10% (774 deaths out of 9098 cases), turning the world's attention to human coronaviruses [9][10][11]. Since then, several other HCoVs were identified; nearly 30 strains were found. The first HCoV strain identified was B814 that was isolated in 1965 [12]. In the post-SARS era, several other HCoVs strains appeared, including HCoV-NL63 in 2004, HCoV-HKU1 in 2005, and 229E and OC43 between 2003 and 2005 [13], which caused mild to moderate upper-respiratory tract illness in humans, resulting in approximately 15–30% of common cold cases [8]. Later in 2012, another human coronavirus with a higher fatality rate (35%) invaded the Middle East and spread to other countries, which was then named the Middle East Respiratory Syndrome coronavirus (MERS-CoV) [14][15][16][17]. Recently, at the end of December 2019, specifically in Wuhan, China, a new coronavirus was discovered in a number of patients suffering from severe pneumonia, resulting in a new disease called coronavirus disease of 2019 (COVID-19), which turned out to be a new type of human coronaviruses and was given the name SARS-CoV-2: severe acute respiratory syndrome coronavirus 2 [18][19][20][21].

Different host-cell receptors are utilized by viral proteins to recognize host cells, such as integrins, angiotensin-converting enzyme 2 (ACE2), sialic acid receptors, dipeptidyl peptidase 4 (DPP4), and glucose regulated protein 78 (GRP78).

2. SARS-CoV-2 Entry Receptors and Potential Therapeutic Targets

2.1. TLR1/2/6 in Proinflammatory Responses

The TLR2 receptor, which recognizes bacterial lipopeptides (LP), collaborates to form functional heterodimers with either TLR1 or TLR6 to mediate intracellular signaling [22][23][24]. TLR2 is regulated in chronic obstructive pulmonary disease (COPD) and predominantly detects invasive Gram-positive bacteria, mycobacteria, and fungi [25][26][27][28]. TLR2 heterodimers with either TLR1 or TLR6 enhanced proinflammatory responses during viral infection by identifying viral glycoproteins [29][30]. This implies a limited function for antiviral immunity [31]. The immunopathological functions played by TLR1 and TLR6 during SARS-CoV-2 infection remain to be clarified [30]. However, increased levels of TLR2 with either TLR1 or TLR6 DAMPs, including beta-defensin-3, named TLR1/2, and the high-mobility group box-1 (HMGB1), named TLR1/2/6, were recorded in peripheral blood mononuclear cells and serum obtained from COVID-19 patients [32][33][34].

The direct binding between DAMPs and the corresponding TLRs can trigger TLR-mediated inflammatory reactions, analogous to that induced by PAMP recognition [35]. Consequently, TLR1/2/6 activation and its consequent signal transduction may play a role in explaining the immunopathological symptoms observed by COVID-19 patients in clinical settings.

2.2. SARS-CoV-2 Infection and TLR3 Role in Antiviral Immunity

TLR3 is required for antiviral immunity because it recognizes and communicates with viral PAMPs, such as double-stranded ribonucleic acid (dsRNA) generated by positive sense-strand RNA and DNA viruses during viral replication [36][37], small interference RNA [38], and inadequate stem structures in single-stranded RNA [39]. Liberated cellular debris, besides the cytoplasmic nucleotides (messenger RNA and dsRNA) and GRP78, activates TLR3 DAMPs from host cells [38][40][41]. TLR3 is unique in that it is the only TLR that interacts solely with TRIF, activating both NF-κβ and interferon-regulatory factor-3 and 7 [36]. This interaction causes pro-inflammatory molecules to be released, such as IL-1β, IL-6, IL-8, and TNF-α, found in the immunopathological screening of COVID-19 patients [42][43]. Direct communication between TLR3 and the SARS-CoV-2 S protein has yet to be explained. TLR3 may recognize SARS-CoV-2 products released during viral replication, indicating that TLR3 may be a therapeutic target that, when activated, may increase antiviral immune responses, decrease viral loads, and promote SARS-CoV-2 blockage [44].

2.3. TLR4 Inhibition and SARS-CoV-2 Entry

TLR4 recognizes lipopolysaccharide (LPS) of bacteria and its activation generally results in the production of chemokines and pro-inflammatory cytokines [45]. Due to the physiological characterization of LPS, the TLR4 receptor is responsible for Gram-negative bacterial immunity [44][46]. TLR4 activation and interaction with viral fusion proteins and glycoproteins, such as those seen in respiratory viruses, have been described [47][48]. TLR4 can react to a variety of DAMPs originating from the host, which have been linked to increased and uncontrolled inflammation in autoimmune illnesses and chronic inflammatory disorders [49][50]. TLR4-mediated inflammation that is unregulated has been associated with immunopathological effects in COVID-19 patients [50]. In computational studies investigating the TLR-binding efficacy of S protein have demonstrated that TRL4 has the highest affinity for the S1 domain of the S protein [51]. As TLR4's ability to suppress pathogens could constitute a novel viral entry route for SARS-CoV-2, TLR4 inhibition as a potential treatment in COVID-19 infection should be examined.

2.4. TLR5 as a Potential SARS-CoV-2 Vaccine Target

During vaccine development and to enhance the vaccine efficacy by tailoring the immune responses, a potent immunomodulatory agent called flagellin, which is a structural whip-like filament dependent on microtubules, has been used as an adjuvant component [52][53] due to its ability to influence pathogenic virulence to enable locomotion in motile Gram-negative and positive bacteria [54][55]. The interaction of flagellin with TLR5 leads to subsequent NF-kβ motivated inflammation through enrolment of MyD88 and has been shown to be an effective immunomodulatory agent [22][56][57][58][59]. The use of flagellin to target TLR5 in the creation of vaccines against viral infections has been studied. However, the interaction of TLR5 with SARS-CoV-2 needs to be investigated. In silico studies showed positive energy for TLR5 and S protein of SARS-CoV-2, indicating a possible association [51].

2.5. TLR7 and TLR8 Role in SARS-CoV-2 Infection

Toll-like receptors 7/8 (TLR7/8) are pattern recognition receptors (PRR) located on intracellular organelles that produce antiviral immunity by recognizing the viral single-stranded RNA (ssRNA) and releasing cytokines, chemokines, IFN-α, IFN-β, and IFN-λ as pro-inflammatory mechanisms [60][61]. Studies have demonstrated TLR7/8′s role in reducing viral replication in HIV-1 [62], influenza [51], and MERS-CoV [63]. When viral ssRNA binds to TLR7/8 upon viral entry, antiviral immunity is activated. The SARS-CoV-2 genome has shown more ssRNA segments that TLR7/8 can detect than the SARS-CoV genome, suggesting SARS-CoV-2 causes innate immune hyperactivation [64]. This observation suggested a strong pro-inflammatory response via TLR7/8 recognition. On the other hand, a larger number of SARS-CoV-2 fragments that TLR7/8 identified suggested that rapid release of type I IFNs by TLR7/8 influences the severity of SARS-CoV-2 by changing dendritic Cell (DC) growth, maturation, and apoptosis, and virus-specific cytotoxic responses produced by T lymphocytes and cytotoxicity of natural killer cells [64]. As DC function has been shown to be reduced, attempts to reverse this negative effect may be effective in Covid-19 treatment [65]. COVID-19 patients showed increased blood levels of pro-inflammatory cytokines and chemokines, which are produced by the TLR7/8 pathways [60]. This could be attributed to an increase in TLR7/8 recognizing antiphospholipid antibodies (aPL) (a TLR7/8 activating DAMP) in COVID-19 patients [43][66][67]. TLR7 and TLR8 activation could be employed to improve viral immunity as a potential therapeutic therapy. Based on data analysis collected from mice models treated with imiquimod following influenza A infection, imiquimod, a dual

TLR7/8 agonist, has been proposed as a viable treatment for COVID-19 patients [68]. Direct infusion of imiquimod into the lungs lowers viral multiplication, avoids pulmonary inflammation and leukocyte infiltration; protects against pulmonary dysfunction worsening; and elevates pulmonary immunoglobulins and bronchiole fluid antibodies (such as IgG1, IgG2a, IgE, and IgM) [69]. Due to its role in increasing antigen-specific antibody production and enhancing the immune response for viral clearance, imiquimod could be used both for COVID-19 therapeutic treatment and as an adjuvant in the SARS-CoV-2 vaccine [70][71].

2.6. C-Lectin Type Receptors Involved with SARS-CoV-2

C-type lectin receptors (CLRs) are a large family of transmembrane-soluble pattern recognition receptors that contain one or more conserved carbohydrate-recognition domains [72][73]. Such receptors can help in the calcium-dependent recognition of glycosylation marks present on pathogens' proteins [74]. CLRs interact with mannose, fucose, and glucan mono- and polysaccharide structures to identify infections [75]. PAMP recognition by CLRs results in pathogen uptake, breakdown, and antigen presentation [76]. CLRs can as well connect with other PRRs, such as TLRs, allowing for the strengthening or weakening of innate immunity inflammatory responses by increasing or decreasing receptor activation and signal transduction [77][78]. In vitro study models have demonstrated a direct relationship between selective CLRs and SARS-CoV-2 spike protein mannosylated and N- and O-glycans [79].

3. Conclusions

The coronavirus disease COVID-19, caused by the SARS-CoV-2 virus, spreads mainly through person-to-person contact. SARS-CoV-2 is one of seven identified human coronaviruses that can cause serious illnesses. SARS-CoV-2 can trigger a respiratory tract infection, ranging from mild to deadly, and can cause respiratory failure, septic shock, pneumonia, heart, and liver complications, and may lead to death.

We covered the history and progression of human coronaviruses in this paper and the various host-cell receptors that may be engaged in the viral entry mechanism, showing that the SARS-CoV-2 virus can use multiple receptors to enter the host-cells. Understanding the mechanism of SARS-CoV-2 infection requires determining the pathway through which the virus components bind to host-cell receptors. The information gathered in this study can be used as a guided tool to investigate how different cell types interact with the SARS-CoV-2 virus, while supported experimental investigations are required to explain the susceptibility differences to the viral infection. Afterward, we could ultimately be able to explain why some people are more susceptible to SARS-CoV-2 infection than others. In addition, it could help researchers understand how to specifically target the SARS-CoV-2 virus with drugs and immunotherapies to treat COVID-19 symptoms and improve the vaccine development research pipeline to prevent the disease.

References

1. Payne, S. Family Coronaviridae. Viruses 2017, 149–158.
2. Pellett, P.E.; Mitra, S.; Holland, T.C. Basics of virology. Handb. Clin. Neurol. 2014, 123, 45–66.
3. Chan, J.F.; To, K.K.; Tse, H.; Jin, D.Y.; Yuen, K.Y. Interspecies transmission and emergence of novel viruses: Lessons fr om bats and birds. Trends Microbiol. 2013, 21, 544–555.
4. Woo, P.C.Y.; Huang, Y.; Lau, S.K.P.; Yuen, K.-Y. Coronavirus Genomics and Bioinformatics Analysis. Viruses 2010, 2, 1 804–1820.
5. Becker, W.B.; McIntosh, K.; Dees, J.H.; Chanock, R.M. Morphogenesis of Avian Infectious Bronchitis Virus and a Relat ed Human Virus (Strain 229E). J. Virol. 1967, 1, 1019–1027.
6. Dillon, C.F.; Dillon, M.B. Multiscale Airborne Infectious Disease Transmission. Appl. Environ. Microbiol. 2021, 87, 02314 –02320.
7. Miłek, J.; Blicharz-Domańska, K. Coronaviruses in avian species—Review with focus on epidemiology and diagnosis in wild birds. J. Vet. Res. 2018, 62, 249–255.
8. Lim, Y.X.; Ng, Y.L.; Tam, J.P.; Liu, D.X. Human Coronaviruses: A Review of Virus-Host Interactions. Diseases 2016, 4, 2 6.
9. Drosten, C.; Preiser, W.; Günther, S.; Schmitz, H.; Doerr, H.W. Severe acute respiratory syndrome: Identification of the etiological agent. Trends Mol. Med. 2003, 9, 325–327.

10. Zhang, W.; Zheng, Q.; Yan, M.; Chen, X.; Yang, H.; Zhou, W.; Rao, Z. Structural characterization of the HCoV-229E fusion core. Biochem. Biophys. Res. Commun. 2018, 497, 705–712.

11. Belouzard, S.; Millet, J.K.; Licitra, B.N.; Whittaker, G.R. Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein. Viruses 2012, 4, 1011–1033.

12. Kapikian, Z. The coronaviruses. Dev. Biol. Stand. 1975, 28, 42–64.

13. Gerna, G.; Campanini, G.; Rovida, F.; Percivalle, E.; Sarasini, A.; Marchi, A.; Baldanti, F. Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. J. Med. Virol. 2006, 78, 938–949.

14. Tyrovolas, S.; El Bcheraoui, C.; Alghnam, S.A.; Alhabib, K.F.; Almadi, M.A.H.; Al-Raddadi, R.M.; Bedi, N.; El Tantawi, M.; Krish, V.S.; Memish, Z.A.; et al. The burden of disease in Saudi Arabia 1990–2017: Results from the Global Burden of Disease Study 2017. Lancet Planet. Health 2020, 4, e195–e208.

15. Al-Dorzi, H.M.; Van Kerkhove, M.D.; Peiris, J.M.; Arabi, Y.M. Middle East respiratory syndrome coronavirus. SARS MERS Other Viral Lung Infect. 2016, 2016, 21–34.

16. Ashour, H.M.; Elkhatib, W.F.; Rahman, M.; Elshabrawy, H.A. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. Pathogens 2020, 9, 186.

17. Zaki, A.M.; Van Boheemen, S.; Bestebroer, T.M.; Osterhaus, A.D.M.E.; Fouchier, R.A.M. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. N. Engl. J. Med. 2012, 367, 1814–1820.

18. Zheng, J. SARS-CoV-2: An Emerging Coronavirus that Causes a Global Threat. Int. J. Biol. Sci. 2020, 16, 1678–1685.

19. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N. Engl. J. Med. 2020, 382, 727–733.

20. Benvenuto, D.; Giovannetti, M.; Ciccozzi, A.; Spoto, S.; Angeletti, S.; Ciccozzi, M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J. Med. Virol. 2020, 92, 455–459.

21. House, N.N.C.; Palissery, S.; Sebastian, H. Corona Viruses: A Review on SARS, MERS and COVID-19. Microbiol. Insights 2021, 14, 11786361211002480.

22. Takeda, K. Toll-like receptors in innate immunity. Int. Immunol. 2004, 17, 1–14.

23. Ozinsky, A.; Underhill, D.; Fontenot, J.D.; Hajjar, A.; Smith, K.D.; Wilson, C.B.; Schroeder, L.; Aderem, A. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between Toll-like receptors. Proc. Natl. Acad. Sci. USA 2000, 97, 13766–13771.

24. Motoi, Y.; Shibata, T.; Takahashi, K.; Kanno, A.; Murakami, Y.; Li, X.; Kasahara, T.; Miyake, K. Lipopeptides are signaled by Toll-like receptor 1, 2 and 6 in endolysosomes. Int. Immunol. 2014, 26, 563–573.

25. Misch, E.A.; Macdonald, M.; Ranjit, C.; Sapkota, B.R.; Wells, R.D.; Siddiqui, M.R.; Kaplan, G.; Hawn, T.R. Human TLR 1 Deficiency Is Associated with Impaired Mycobacterial Signaling and Protection from Leprosy Reversal Reaction. PLoS Negl. Trop. Dis. 2008, 2, e231.

26. Buwitt-Beckmann, U.; Heine, H.; Wiesmüller, K.-H.; Jung, G.; Brock, R.; Akira, S.; Ulmer, A.J. TLR1- and TLR6-independent Recognition of Bacterial Lipopeptides. J. Biol. Chem. 2006, 281, 9049–9057.

27. Fuchs, K.; Gloria, Y.C.; Wolz, O.; Herster, F.; Sharma, L.; Dillen, C.A.; Täumer, C.; Dickhöfer, S.; Bittner, Z.; Dang, T.; et al. The fungal ligand chitin directly binds TLR 2 and triggers inflammation dependent on oligomer size. EMBO Rep. 2018, 19, e201846065.

28. Pellerin, A.; Otero, K.; Czerkowicz, J.M.; Kerns, H.M.; Shapiro, R.I.; Ranger, A.M.; Otipoby, K.L.; Taylor, F.R.; Cameron, T.O.; Viney, J.L.; et al. Anti- BDCA 2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. EMBO Mol. Med. 2015, 7, 464–476.

29. Boehme, K.W.; Guerrero, M.; Compton, T. Human Cytomegalovirus Envelope Glycoproteins B and H Are Necessary for TLR2 Activation in Permissive Cells. J. Immunol. 2006, 177, 7094–7102.

30. Cuevas, C.D.; Ross, S.R. Toll-Like Receptor 2-Mediated Innate Immune Responses against Junín Virus in Mice Lead to Antiviral Adaptive Immune Responses during Systemic Infection and Do Not Affect Viral Replication in the Brain. J. Virol. 2014, 88, 7703–7714.

31. Farhat, K.; Riekenberg, S.; Heine, H.; Debarry, J.; Lang, R.; Mages, J.; Buwitt-Beckmann, U.; Röschmann, K.; Jung, G.; Wiesmüller, K.-H.; et al. Heterodimerization of TLR2 with TLR1 or TLR6 expands the ligand spectrum but does not lead to differential signaling. J. Leukoc. Biol. 2008, 83, 692–701.

32. Matsumiya, M.; Stylianou, E.; Griffiths, K.; Lang, Z.; Meyer, J.; Harris, S.A.; Rowland, R.; Minassian, A.; Pathan, A.A.; Fletcher, H.; et al. Roles for Treg Expansion and HMGB1 Signaling through the TLR1-2-6 Axis in Determining the Magnitude of the Antigen-Specific Immune Response to MVA85A. PLoS ONE 2013, 8, e67922.

33. Chiodo, F.; Bruijns, S.C.; Rodriguez, E.; Li, R.E.; Molinaro, A.; Silipo, A.; Di Lorenzo, F.; Garcia-Rivera, D.; Valdes-Balbin, Y.; Verez-Bencomo, V.; et al. Novel ACE2-Independent Carbohydrate-Binding of SARS-CoV-2 Spike Protein to Host Lectins and Lung Microbiota. bioRxiv 2020.

34. Feinberg, H.; Jégouzo, S.A.F.; Rex, M.J.; Drickamer, K.; Weis, W.I.; Taylor, M.E. Mechanism of pathogen recognition by human dectin-2. J. Biol. Chem. 2017, 292, 13402–13414.

35. Komai, K.; Shichita, T.; Ito, M.; Kanamori, M.; Chikuma, S.; Yoshimura, A. Role of scavenger receptors as damage-associated molecular pattern receptors in Toll-like receptor activation. Int. Immunol. 2017, 29, 59–70.

36. Alexopoulou, L.; Holt, A.C.; Medzhitov, R.; Flavell, R.A. Recognition of double-stranded RNA and activation of NF-κB by Toll-like receptor 3. Nat. Cell Biol. 2001, 413, 732–738.

37. Weber, F.; Wagner, V.; Rasmussen, S.B.; Hartmann, R.; Paludan, S.R. Double-Stranded RNA Is Produced by Positive-Strand RNA Viruses and DNA Viruses but Not in Detectable Amounts by Negative-Strand RNA Viruses. J. Virol. 2006, 80, 5059–5064.

38. Karikó, K.; Bhuyan, P.; Capodici, J.; Weissman, D. Small Interfering RNAs Mediate Sequence-Independent Gene Suppression and Induce Immune Activation by Signaling through Toll-Like Receptor 3. J. Immunol. 2004, 172, 6545–6549.

39. Tatematsu, M.; Nishikawa, F.; Seya, T.; Matsumoto, M. Toll-like receptor 3 recognizes incomplete stem structures in single-stranded viral RNA. Nat. Commun. 2013, 4, 1833.

40. Karikó, K.; Ni, H.; Capodici, J.; Lamphier, M.; Weissman, D. mRNA Is an Endogenous Ligand for Toll-like Receptor 3. J. Biol. Chem. 2004, 279, 12542–12550.

41. Suresh, M.V.; Thomas, B.; Machado-Aranda, D.; Dolgachev, V.A.; Ramakrishnan, S.K.; Talarico, N.; Cavassani, K.; Sherman, M.A.; Hemmila, M.R.; Kunkel, S.L.; et al. Double-Stranded RNA Interacts with Toll-Like Receptor 3 in Driving the Acute Inflammatory Response Following Lung Contusion. Crit. Care Med. 2016, 44, e1054–e1066.

42. Zhou, Y.; Zhang, R.; Wang, G.; Wang, A.; Zhong, C.; Zhang, M.; Li, H.; Xu, T.; Zhang, Y. Coexistence effect of hypertension and angiotensin II on the risk of coronary heart disease: A population-based prospective cohort study among Inner Mongolians in China. Curr. Med. Res. Opin. 2019, 35, 1473–1478.

43. Hurst, J.; Prinz, N.; Lorenz, M.; Bauer, S.; Chapman, J.; Lackner, K.J.; von Landenberg, P. TLR7 and TLR8 ligands and antiphospholipid antibodies show synergistic effects on the induction of IL-1β and caspase-1 in monocytes and dendritic cells. Immunobiology 2009, 214, 683–691.

44. Gadanec, L.; McSweeney, K.; Qaradakhi, T.; Ali, B.; Zulli, A.; Apostolopoulos, V. Can SARS-CoV-2 Virus Use Multiple Receptors to Enter Host Cells? Int. J. Mol. Sci. 2021, 22, 992.

45. Vaure, C.; Liu, Y. A Comparative Review of Toll-Like Receptor 4 Expression and Functionality in Different Animal Species. Front. Immunol. 2014, 5, 316.

46. Park, B.S.; Lee, J.-O. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp. Mol. Med. 2013, 45, e66.

47. Marr, N.; Turvey, S.E. Role of human TLR4 in respiratory syncytial virus-induced NF-κB activation, viral entry and replication. Innate Immun. 2012, 18, 856–865.

48. Kurt-Jones, E.A.; Popova, L.; Kwinn, L.A.; Haynes, L.M.; Jones, L.P.; Tripp, R.; Walsh, E.E.; Freeman, M.W.; Golenbock, D.T.; Anderson, L.J.; et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat. Immunol. 2000, 1, 398–401.

49. Gong, T.; Liu, L.; Jiang, W.; Zhou, R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat. Rev. Immunol. 2020, 20, 95–112.

50. Gao, W.; Xiong, Y.; Li, Q.; Yang, H. Inhibition of Toll-Like Receptor Signaling as a Promising Therapy for Inflammatory Diseases: A Journey from Molecular to Nano Therapeutics. Front. Physiol. 2017, 8, 508.

51. Choudhury, A.; Mukherjee, S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. J. Med. Virol. 2020, 92, 2105–2113.

52. Ramos, H.C.; Rumbo, M.; Sirard, J.-C. Bacterial flagellins: Mediators of pathogenicity and host immune responses in mucosa. Trends Microbiol. 2004, 12, 509–517.

53. Song, W.S.; Jeon, Y.J.; Namgung, B.; Hong, M.; Yoon, S.-I. A conserved TLR5 binding and activation hot spot on flagellin. Sci. Rep. 2017, 7, 40878.

54. Reed, S.G.; Orr, M.; Fox, C. Key roles of adjuvants in modern vaccines. Nat. Med. 2013, 19, 1597–1608.

55. Duthie, M.; Windish, H.P.; Fox, C.; Reed, S.G. Use of defined TLR ligands as adjuvants within human vaccines. Immunol. Rev. 2010, 239, 178–196.

56. Akira, S.; Uematsu, S.; Takeuchi, O. Pathogen recognition and innate immunity. Cell 2006, 124, 783–801.

57. Hajam, I.A.; Dar, P.; Shahnawaz, I.; Jaume, J.C.; Lee, J.H. Bacterial flagellin—A potent immunomodulatory agent. Exp. Mol. Med. 2017, 49, e373.

58. Felgner, S.; Spöring, I.; Pawar, V.; Kocijancic, D.; Preusse, M.; Falk, C.; Rohde, M.; Häussler, S.; Weiss, S.; Erhardt, M. The immunogenic potential of bacterial flagella for Salmonella -mediated tumor therapy. Int. J. Cancer 2019, 147, 448–460.

59. Georgel, A.-F.; Cayet, D.; Pizzorno, M.A.; Rosa-Calatrava, M.; Paget, C.; Sencio, V.; Dubuisson, J.; Trottein, F.; Sirard, J.-C.; Carnoy, C. Toll-like receptor 5 agonist flagellin reduces influenza A virus replication independently of type I interfe ron and interleukin 22 and improves antiviral efficacy of oseltamivir. Antivir. Res. 2019, 168, 28–35.

60. Grassin-Delyle, S.; Abrial, C.; Salvator, H.; Brollo, M.; Naline, E.; DeVillier, P. The Role of Toll-Like Receptors in the Pro duction of Cytokines by Human Lung Macrophages. J. Innate Immun. 2020, 12, 63–73.

61. Yang, K.; Puel, A.; Zhang, S.; Eidenschenk, C.; Ku, C.-L.; Casrouge, A.; Picard, C.; von Bernuth, H.; Senechal, B.; Plan coulaine, S.; et al. Human TLR-7-, -8-, and -9-Mediated Induction of IFN-α/β and -λ Is IRAK-4 Dependent and Redunda nt for Protective Immunity to Viruses. Immunity 2005, 23, 465–478.

62. Casalino, L.; Gaieb, Z.; Goldsmith, J.A.; Hjorth, C.K.; Dommer, A.C.; Harbison, A.M.; Fogarty, C.A.; Barros, E.P.; Taylor, B.C.; McLellan, J.S.; et al. Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein. ACS Central Sci. 2020, 6, 1722–1734.

63. Channappanavar, R.; Fehr, A.R.; Zheng, J.; Wohlford-Lenane, C.; Abrahante, J.E.; Mack, M.; Sompallae, R.; McCray, P.B.; Meyerholz, D.K.; Perlman, S. IFN-I response timing relative to virus replication determines MERS coronavirus infe ction outcomes. J. Clin. Investig. 2019, 129, 3625–3639.

64. Moreno-Eutimio, M.A.; López-Macías, C.; Pastelin-Palacios, R. Bioinformatic analysis and identification of single-strand ed RNA sequences recognized by TLR7/8 in the SARS-CoV-2, SARS-CoV, and MERS-CoV genomes. Microbes Infect. 2020, 22, 226–229.

65. Campana, P.; Parisi, V.; Leosco, D.; Bencivenga, D.; Della Ragione, F.; Borriello, A. Dendritic Cells and SARS-CoV-2 In fection: Still an Unclarified Connection. Cells 2020, 9, 2046.

66. Prinz, N.; Clemens, N.; Strand, D.; Pütz, I.; Lorenz, M.; Daiber, A.; Stein, P.; Degreif, A.; Radsak, M.; Schild, H.; et al. A ntiphospholipid antibodies induce translocation of TLR7 and TLR8 to the endosome in human monocytes and plasmac ytoid dendritic cells. Blood 2011, 118, 2322–2332.

67. Döring, Y.; Hurst, J.; Lorenz, M.; Prinz, N.; Clemens, N.; Drechsler, M.D.; Bauer, S.; Chapman, J.; Shoenfeld, Y.; Blank, M. Human antiphospholipid antibodies induce TNFα in monocytes via Toll-like receptor 8. Immunobiology 2010, 215, 2 30–241.

68. Angelopoulou, A.; Alexandris, N.; Konstantinou, E.; Mesiakaris, K.; Zanidis, C.; Farsalinos, K.; Poulas, K. Imiquimod—A toll like receptor 7 agonist—Is an ideal option for management of COVID 19. Environ. Res. 2020, 188, 109858.

69. To, E.E.; Erlich, J.; Liong, F.; Luong, R.; Liong, S.; Bozinovski, S.; Seow, H.; O'Leary, J.J.; Brooks, D.A.; Vlahos, R.; et a l. Intranasal and epicutaneous administration of Toll-like receptor 7 (TLR7) agonists provides protection against influenz a A virus-induced morbidity in mice. Sci. Rep. 2019, 9, 2366.

70. Li, C.; To, K.; Zhang, J.; Lee, A.C.Y.; Zhu, H.; Mak, W.W.N.; Hung, I.F.N.; Yuen, K.-Y. Co-stimulation with TLR7 Agonist I miquimod and Inactivated Influenza Virus Particles Promotes Mouse B Cell Activation, Differentiation, and Accelerated Antigen Specific Antibody Production. Front. Immunol. 2018, 9, 2370.

71. Zhang, J.; Li, C.; To, K.; Zhu, H.-S.; Lee, A.C.Y.; Li, C.-G.; Chan, J.F.-W.; Hung, I.F.N.; Yuen, K.-Y. Toll-Like Receptor 7 Agonist Imiquimod in Combination with Influenza Vaccine Expedites and Augments Humoral Immune Responses again st Influenza A(H1N1)pdm09 Virus Infection in BALB/c Mice. Clin. Vaccine Immunol. 2014, 21, 570–579.

72. Egea, S.C.; Dickerson, I.M. Direct Interactions between Calcitonin-Like Receptor (CLR) and CGRP-Receptor Compone nt Protein (RCP) Regulate CGRP Receptor Signaling. Endocrinology 2012, 153, 1850–1860.

73. Geijtenbeek, T.B.H.; Gringhuis, S.I. C-type lectin receptors in the control of T helper cell differentiation. Nat. Rev. Immu nol. 2016, 16, 433–448.

74. Gao, C.; Zeng, J.; Jia, N.; Stavenhagen, K.; Matsumoto, Y.; Zhang, H.; Li, J.; Hume, A.J.; Mühlberger, E.; van Die, I.; et al. SARS-CoV-2 Spike Protein Interacts with Multiple Innate Immune Receptors. bioRxiv 2020.

75. Lee, R.T.; Hsu, T.-L.; Huang, S.K.; Hsieh, S.-L.; Wong, C.-H.; Lee, Y.C. Survey of immune-related, mannose/fucose-bin ding C-type lectin receptors reveals widely divergent sugar-binding specificities. Glycobiology 2010, 21, 512–520.

76. Schreibelt, G.; Klinkenberg, L.J.J.; Cruz, L.J.; Tacken, P.J.; Tel, J.; Kreutz, M.; Adema, G.J.; Brown, G.D.; Figdor, C.G.; de Vries, I.J.M. The C-type lectin receptor CLEC9A mediates antigen uptake and (cross-)presentation by human blood BDCA3+ myeloid dendritic cells. Blood 2012, 119, 2284–2292.

77. Gorjestani, S.; Darnay, B.G.; Lin, X. Tumor Necrosis Factor Receptor-associated Factor 6 (TRAF6) and TGFβ-activated Kinase 1 (TAK1) Play Essential Roles in the C-type Lectin Receptor Signaling in Response to Candida albicans Infectio n. J. Biol. Chem. 2012, 287, 44143–44150.

78. Gantner, B.N.; Simmons, R.M.; Canavera, S.J.; Akira, S.; Underhill, D.M. Collaborative Induction of Inflammatory Resp onses by Dectin-1 and Toll-like Receptor 2. J. Exp. Med. 2003, 197, 1107–1117.

79. Amraie, R.; Napoleon, M.A.; Yin, W.; Berrigan, J.; Suder, E.; Zhao, G.; Olejnik, J.; Gummuluru, S.; Muhlberger, E.; Chit alia, V.; et al. CD209L/L-SIGN and CD209/DC-SIGN act as receptors for SARS-CoV-2 and are differentially expressed i n lung and kidney epithelial and endothelial cells. bioRxiv 2020.
