Immune System: A Determining Factor in the Severity, Pathogenesis, and Treatment of the SARS-CoV-2 Infection

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ABSTRACT

SARS-CoV-2 is the enveloped virus with a positive sense, single-stranded RNA genome which causes a new outbreak of acute respiratory disease and deadly epidemics. Bat is the important reservoir host of SARS-CoV-2. The robust immune system of bats turns viral strains with mild pathogenesis into a highly pathogenic species for humans. The interaction between SARS-CoV-2 and the immune system of the hosts plays a great role in the fate of the SARS-CoV-2 infection. Immunopathology of the SARS-CoV-2 infection needs to be taken into consideration in the development of preventative and therapeutic methods. Based on the accumulated data and knowledge on the previous related articles, this review hopes to help understand the role of the immune response in virulence exacerbation, pathogenesis, and ultimately immunological treatment of the SARS-CoV-2 infection.

KEYWORDS: SARS-CoV-2; Immune response; Pathogenesis; Immunotherapy, Coronavirus

INTRODUCTION

Viral infections are particularly important because they spread rapidly among people and can cause large epidemics or even pandemics. In the past few years, viral respiratory diseases such as influenza virus infection, middle eastern respiratory syndrome (MERS-CoV), highly pathogenic avian influenza, and severe acute respiratory syndrome (SARS-CoV) coronaviruses threat human health globally [1]. a short time ago, in November 2019, a novel coronavirus (SARS-CoV-2) was detected in Wuhan City which caused the outbreak of respiratory disease and death [2]. SARS-CoV-2 virus, like other Coronaviruses (CoVs), is the enveloped virus with a positive sense, single-stranded RNA genome [3]. CoVs are potentially lethal pathogens, characterized by the presence of spike proteins on the viral surface. they could cause acute respiratory distress syndrome (ARDS) and are associated with high mortality rates [4]. the SARS-CoV-2 infection has a probable asymptomatic incubation period about two weeks during which the virus can be transmitted [5]. Based on recent reports, it's clear that symptomatic SARS-CoV-2 infection mainly consists of three phases, including a starting phase, spanning the acquisition of the virus and subsequent viremia; and in many but not all patients an accelerating phase, when virus-induced secondary damages occur in the lungs, the heart, the gastrointestinal tract, and even an overall inflammatory storm. The third phase is the final recovery phase [6]. The general symptoms of the SARS-CoV-2 infection are fever, fatigue, and respiratory symptoms, including cough, sore throat, and shortness of breath [7,8]. SARS-CoV-2 has evolved specific mechanisms to escape the innate and adaptive immune responses such as reducing interferon subtypes expression and disrupting their signaling pathways which are the initial factors to coronavirus infection pathogenesis [9]. It seems the response of the immune system to the virus plays an important role in causing the disease as well as its severity. The innate immune response to tissue damage caused by the virus could lead to ARDS which is the leading cause of mortality [10]. Additionally, the levels of inflammatory cytokines especially IL-1, TNF are high which are strong inducers of HA-

synthase-2 (HAS2) in EpCAM+ lung alveolar epithelial cells, CD31+ endothelium, and fibroblasts [11]. During the incubation period, an effective immune response plays a substantial role in the outcome of the disease. A specific adaptive immune response can eliminate the virus and preclude disease progression to severe stages. Therefore, strategies to boost immune responses (anti-sera or pegylated IFNα) at this stage are certainly important [12]. On the other hand, it is determined when the virus, once severe lung damage occurs, efforts should be made to suppress the immune system and to manage the inflammatory mediators in order to treat the infection. It seems that the SARS-CoV-2 infection presents a virological and immunological conundrum. A growing body of reports revealed that the host immune response rather than direct SARS-CoV-2 damage primarily accounts for the pathologic changes. Therefore, finding the host immune system-related factors as well as virus-dependent factors is very important because they regulate the severity of the virus-associated disease. In addition, understanding the induced immune responses in SARS-CoV-2 infection can lead to the development of novel preventive and therapeutic strategies. The present review article, therefore, provides a brief overview of the contribution of the immune system in virulence, pathogenesis, and treatment of SARS-CoV-2.

Bat Immune system and CoVs virulence

Bats are a large group of mammals that have the capability of flight and also have a wide geographical distribution [13]. Studies have shown that bats are important reservoir hosts of viruses that cause outbreaks and deadly epidemics in recent years [14]. Bats demonstrate no obvious disease symptoms upon infection with pathogens that are highly virulent in non-Volant mammals. The importance of bats as a source of emerging viruses has been proven from numerous studies in the last two decades [15]. Bats may have a robust and effective immune system that turns viral strains with mild pathogenesis into a highly pathogenic species for humans [16]. Little is known about the bat's immune system, although various studies have shown that the bat's immune system is similar to the evolved mammalian immune system. B- and T-lymphocyte-like cells and macrophages were identified in the bone marrow of bats, denoting that lymphoid development are generally similar in bats and other mammals [17,18].

Additionally, immunoglobulin G (IgG), IgA, and IgM have been purified from sera of some kinds of bats [19]. Serological assays that detect IgG antibodies to Hendra virus, severe acute respiratory syndrome coronavirus (SARS- CoV)-like viruses and Ebola viruses in bats indicate that some virus-specific adaptive T- and B-cell responses occur despite persistent virus infection [20-22]. One of the challenging scientific questions is why many of the bat-borne zoonotic viruses are so lethal when they spill over into human and/ or livestock animal populations. With our current knowledge, it is difficult to answer this question due to the lack of research tools for immunology and pathogenesis studies in bats. Several recent studies, however, start to reveal that bats may have evolved a more balanced innate defense system.

On the other hand, bats have an elevated levels of certain defense genes such as type I interferon and related pathways in order [23] to apoptosis [24] the infected cells at the same time. Bats exhibit more immune tolerance in different pathways, from inflammation [25] NK cell activation [26]. Bats employ a set of species-specific mechanisms to control viruses, which include constitutive expression of the antiviral cytokine, IFN-α [23]. Unlike human antiviral cytokines, IFN-α, that are produced in the presence of viral RNA or DNA in the cytoplasm, bat antiviral cytokines are expressed constitutively [27] which could achieve more rapid within-host transmission rates without causing pathology to bat [16]. Viruses that are affected and adapted to the immune system of bats can generate extreme virulence upon spillover to other organisms such as humans that have different immune response mechanisms. Therefore, the immune system plays a critical role in increasing virulence of cross-species pathogens such as SARS, MERS, Ebola, and Most probably even, the SARS-CoV-2 virus.

Immunopathogenesis of the SARS-CoV-2 Virus Infection

Clinical symptoms in infected people with emerging coronavirus infection are very varied from person to person. The variability in the severity of the disease in different individuals appears to be due to differences in the immune response. On the other hand, it is assumed that pulmonary damage in the SARS-CoV-2 virus infection is caused by immune-pathological factors as well as direct viral effects. The innate immune system is the first line of the immune defense against infectious agents when they enter the body. The cells of innate immune such as NK cells, subsets of DCs, and innate-like B cells can react to vari¬ous lung viral infections [28]. Identifying the invasion of the viruses is the initial and critical step of the immune response. It is known that pathogen-associated molecular patterns (PAMPs) including endosomal RNA receptors, TLR3 (double-stranded RNA) and TLR7 (single-stranded RNA) and the cytosolic RNA sensor, RIG-I (single-stranded and short double-stranded RNA) and MDA5 (long double-stranded RNA) need to recognize the invasion of RNA viruses such as coronavirus. This recognition event leads to activation of the down¬stream signaling cascade in the nuclei of the cells expressing PAMPs. Eventually, the expression of type I IFN, IFN-α/β, and pro-inflammatory cytokines increases which can suppress viral replication, regulate the cell growth, and activate the immune system [29,30]. But type I IFN production in coronavirus infection is much lower and is delayed compared to other IFN-Inducing Viruses. In fact, the disruption of IFN production as well as IFN -related signaling pathways is the defense mechanism of the coronavirus to escape the immune response [9,31]. The common immune-clinical features of SARS-CoV-2 infected patients of ICU including lymphopenia, neutrophilia, cytokine storm (especially increased serum IL-6) and, increased C - reactive protein [32,33]. Production of high levels of pro-inflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα can initiate viral sepsis and inflam¬matory-induced lung injury which lead to pneumonitis, acute respiratory distress syndrome. The clinical signs of the coronavirus- related diseases are the same, but the severity of SARS and MERS is greater than that of SARS-CoV-2 infection [7,8]. The clinical features of SARS-CoV-2 infection suggesting a potential cytokine storm-mediated coronavirus related disease severity [33,34]. It is speculated that the delayed production of type I IFN leads to disruption of virus control in the early stages of infection, but subsequent overproduction of type I IFN type I leads to excessive Induction of inflammatory immune cells i.e., neutrophils. In fact, immunoinflammatory lung disorders such as ARDS caused by virus infection is caused by the hyper-production of neutrophil pro-inflammatory cytokines [35,36]. A similar scenario is predicted with varying degrees of immune dysregulation for the SARS-CoV-2 virus infection [5]. In general, it can be concluded that the lung damaged cells which produce in SARS-CoV-2 infection, initiate the severe inflammatory cascade that is mediated by pro-inflammatory cells such as macrophages and granulocytes [10].

Immune responses to the SARS-CoV-2 Virus Infection

Mucosal parts of the body, especially the respiratory tract mucosa, are constantly exposed to the external environment, making the lung a vulnerable organ to a range of illnesses, especially viral infectious diseases such as SARS-CoV-2 infection. Mucosal SARS-CoV-2 infection plays a critical role not only in virus pathogenesis but also in the virus transmission [37]. Mucous Exposure to SARS-CoV-2 can initiate board, local and systemic, cellular/humoral immune responses at specific mucosa-associated lymphoid tissue (MALT) [38].

In humans, MALT is populated by dendritic cells (DCs), macrophages (MQ), T cells, and B cells. Antigen presented by DC at the infected mucosa can activate T and B cells in situ. Furthermore, DCs can also migrate and also induce systemic immunity [37]. In coronavirus related-infections including SARS-CoV-2 virus infection, like any other viral infection, a T-helper type 1 (Th1) pattern of CD4 T cells play an important controlling role. T-helper cells orchestrate the overall function of the immune system by producing various cytokines. In addition, cytotoxic T cells can kill the cell harboring viruses.

Although the cytotoxic T cells cannot prevent Infectious agents' entry, they contribute to the pathogen clearance by identifying and killing infected cells [39]. Apart from the cell-mediated immune response, the humoral immune response is also induced after viral mucosal infection. Mucosal B cells secrete antigen-specific secretory IgA antibody (sIgA) that is important for effective mucosal immunity. In fact, sIgA effectively neutralize infectious agents and their toxic products on the mucosal surfaces [40]. Furthermore, humoral immune response plays a protective role, limiting infection, by the production of long-lasting specific IgG [41,42].

HLA AND SARS-COV-2

The human leukocyte antigen (HLA) system is a gene complex encoding the highly polymorphic cell-surface proteins, major histocompatibility complex (MHC) proteins. MHC molecules are key to the control of the specificity of antigen presentation to the human immune system. MHC class I (A, B, and C) present peptides from inside the cell. In contrast, MHC class II (DP, DM, DO, DQ, and DR) usually present foreign antigens such as viruses to T-helper lymphocytes which then stimulate cellular and humoral immunity to eliminate the pathogen.

On the other hand, HLA is the important candidates for genetic susceptibility to infectious diseases [43]. In fact, for the development of the protective immune response, the host should have appropriate HLA that elicits an effective antiviral immune response. Genetic background variations are well-known to contribute to individual differences in the immune response to pathogens [44] because, antigen receptors, on T-lymphocytes, recognize the conformational structure of the specific HLA together with the associated foreign antigen peptides. Therefore, different HLA haplotypes in individuals may be associated with sensitivity or even resistance to an infectious agent [45]. The consensus among scientists is that the susceptibility to various infectious diseases such as influenza, HIV, hepatitis B, and tuberculosis is associated with specific HLA. Based on this evidence, it is hypothesized that the anti-SARS-CoV-2 immunity and even the variation in disease severity among individuals may be due to diversity in HLA loci [12,46].

AGE-DEPENDENT IMMUNE RESPONSE AND SARS-COV-2

There is a complicating data concerning SARS-CoV-2 infected persons which explaining why it happened is breathtaking. Severe and fatal SARS-CoV-2 infections are more common in the elderly and immunocompromised individuals, as well as in infants. In contrast, healthy children usually show no signs of infection and are actually carriers of the disease. At first glance, it is clear that the body's immune system plays a key role in the severity of the symptoms of the SARS-CoV-2 infected people [47,48]. It is completely defined that the exaggerated inflammatory response is associated with progression to organ dysfunction and failure. It has been observed that some patients, especially the old, weren't able to turn off their inflammatory response, leading immune cells and inflammation-inducing molecules known as cytokines to flood into the lungs which are known as cytokine storm [49]. Studies have shown that age-associated immune deficiency in mucosal and systemic immunity is not concurrent in the elderly. Mucosal immunity is down-regulated earlier in the elderly [50]. Thus, the elderly population has increased susceptibility to severe viral pulmonary disease and also increased mortality [51]. It seems that innate immunity is the initial and pivotal controlling factor for coronavirus related- disease outcome, because a mild disease has been reported in young people with healthy immune systems who do not have an underlying disease such as hypertension, diabetes, and cardiovascular disease [8]. In very young children the story is different, the innate and acquired immune system of infants are weak, which may be due to various reasons, such as reduced immune responses which leads to ineffective adaptive immune responses, the lack of immune memory as a result of the lack of prior pathogens exposure, CD4 and CD8 lymphocytes dysfunction, the similarity of the immunological pattern of infants to the fetus, which is Th2 (a successful Pregnancy is associated with Th2 immunological pattern in the uterine environment) [52,53]. Additionally, Primary airway epithelial cells from infant animals demonstrated decreased secretion of IFN-α and increased viral replication [54]. Infants had a significantly high level of pro-inflammatory cytokines which are associated with immune-pathologic changes during viral infection. Very young children have an immunologic predisposition to enhanced inflammation which is responsible for the morbidity of the infant [55]. Furthermore, it has been documented that the production of IL-12 is limited in young children after PRR stimulation [56]. By the way, B-cell maturation and antibody production and even response to the vaccine are ineffective in the newborn infants [57]. It has been recently reported that maternal antibodies may interfere with the humoral immune responses of the infants [58]. As a result, the impaired humoral and cellular immune systems influence the immune responses which lead to reduced viral clearance. It makes infants vulnerable to infectious agents.

IMMUNOLOGICAL MECHANISMS FOR THE TREATMENT OF CORONAVIRUS

The mortality rate of SARS-CoV-2 infection is approximately 3·7% [59]. Therefore, there is an urgent need for a therapeutic strategy for saving lives in the world. Since the main cause of death in SARS-CoV-2 infected patients is immune regulation and cytokine release syndrome, a therapeutic approach to immune system modulation can be helpful. Herein, we discuss the newly proposed methods for SARS-CoV-2 infection treatment. This section will be restricted to attempts to use immunological methods in the treatment of SARS-CoV-2 infection.

One of the main causes of the severe form of SARS-CoV-2 infection is the cytokine storm. It seems blocking the signaling pathways of the pro-inflammatory cytokines such as IL-6, IL-1, and TNF can modulate the severity of the SARS-CoV-2 infection [60]. Based on the released evidence, the mesenchymal stem cells transfusion as a cell-based therapeutic strategy can improve the survival of SARS-CoV-2 infected people by modulating the immune system and repair of the damaged lung tissue [61,62]. A high-dose intravenous immunoglobulin (IVIg) administered, passive immunization, at the early stage of clinical deterioration could successfully improve the outcome of SARS-CoV-2 infection. The mechanism of action of the IVIg includes viremia suppression, acceleration of infected cell clearance, and enhancement of opsonization [6]. Another possibility includes Leronlimab, humanized anti CCR5 monoclonal antibody which has shown Therapeutic effects in deadly SARS-CoV-2 infection. The manufacturer claims that CCR5 antagonists can restore the immune cell number/function and relieve the inflammation [63]. Recently, an epidemiological study has shown that the survival of SARS-CoV-2 infected patients in countries receiving the Bacillus Calmette-Guérin (BCG) vaccine is higher than in countries that do not receive the BCG vaccine [64]. Clinical studies have shown that people who were previously BCG-vaccinated may be resistant to viral infections. A clinical trial demonstrated BCG-vaccination, significantly reduces the risk of respiratory tract infection in elderly people by increasing the IFN-γ and IL-10 levels [65]. In general immunological mechanisms involved in the induction of non-specific resistance to viral infections by BCG-vaccination include enhancement of non-specific memory in innate immune cells, induction of non-specific Th1 and Th17 responses, activation of Treg, activation of non-targeted antigens specific CD4+ and CD8+ memory cells. The BCG-vaccine is currently being studied as a promising candidate for the prevention and treatment of SARS-CoV-2 infection [66-69].

CONCLUSION

There is a lot of ignorance about the origin and virulence factor of SARS-CoV-2. But according to the published articles and reports, it seems that the real problem with SARS-CoV-2 is the host immune system. In this way, the bat's immune system increases the virulence of the virus, and in humans, the immune system's response to SARS-CoV-2 increases the pathogenesis and disease severity. The pathogenesis of the virus is related to immunological factors such as the innate immune responses, the paradigm of cellular immune responses (Th1, Th2, and Th17), humoral immune responses (neutralizing antibody) as well as production of pro-inflammatory/anti-inflammatory cytokines. The speed and strength of the immune system responses in people cause different clinical symptoms. Some people are the only carriers of the SARS-CoV-2 without any clinical symptoms, while others die from the SARS-CoV-2 infection. Finally, it can be concluded that the use of new therapeutic methods, especially Immune system-based therapies, to modulate immune responses can be the most effective strategy to the treatment of SARS-CoV-2 infection. The bottom line is that immunological panacea can heal immune-mediated diseases such as the SARS-CoV-2 infection.

REFERENCES

1. Hilgenfeld R, Peiris M (2013) From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antiviral Res 100(1): 286-295.

2. Organization WH (2020) Laboratory testing of human suspected cases of novel coronavirus (nCoV) infection: interim guidance, 10 January 2020. World Health Organization; 2020.

3. Pradesh U, Upadhayay PDD, Vigyan PC (2014) Coronavirus infection in equines: A review. Asian J Anim Vet Adv 9(3): 164-176.

4. Graham RL, Donaldson EF, Baric RS (2013) A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol 11(12): 836-848.

5. Prompetchara E, Ketloy C, Palaga T (2020) Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J allergy Immunol 31(1): 1-9.

6. Cao W, Liu X, Bai T, Fan H, Hong K, et al. (2020) High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. Open Forum Infec Dis 7(3): ofaa102.

7. Chan JF, Yuan S, Kok KH, To KK, Chu H, et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet 395(10223): 514-523.

8. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet 395(10223): 497-506.

9. Scagnolari C, Trombetti S, Cicetti S, Antonelli S, Selvaggi C, et al. (2008) Severe acute respiratory syndrome coronavirus elicits a weak interferon response compared to traditional interferon-inducing viruses. Intervirology 51(4): 217-223.

10. Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet respiratory medicine 8(4): 420-422.

11. Bell TJ, Brand OJ, Morgan DJ, Salek-Ardakani S, Jagger C, et al. (2019) Defective lung function following influenza virus is due to prolonged, reversible hyaluronan synthesis. Matrix Biol 80: 14-28.

12. Shi Y, Wang Y, Shao C, Huang J, Gan J, et al. (2020) COVID-19 infection: the perspectives on immune responses. Cell Death Differ 27(5): 1451-1454.

13. Hu B, Ge X, Wang LF, Shi Z (2015) Bat origin of human coronaviruses. Virol J 12(1): 221.

14. Schountz T, Baker ML, Butler J, Munster V (2017) Immunological control of viral infections in bats and the emergence of viruses highly pathogenic to humans. Frontiers in immunology 8: 1098.

15. Brook CE, Dobson AP (2015) Bats as 'special' reservoirs for emerging zoonotic pathogens. Trends Microbiol 23(3): 172-180.

16. Brook CE, Boots M, Chandran K, Dobson AP, Drosten C, et al. (2020) Accelerated viral dynamics in bat cell lines, with implications for zoonotic emergence. eLife 9: e48401.

17. Sarkar SK, Chakravarty AK (1991) Analysis of immunocompetent cells in the bat, *Pteropus giganteus*: isolation and scanning electron microscopic characterization. Dev Comp Immunol 15(4): 423-430.

18. Chakravarty AK, Sarkar SK (1994) Immunofluorescence analysis of immunoglobulin bearing lymphocytes in the Indian fruit bat: *Pteropus giganteus*. Lymphology 27(2): 97-104.

19. McMurray DN, Stroud J, Murphy JJ, Carlomagno MA, Greer DL (1982) Role of immunoglobulin classes in experimental histoplasmosis in bats. Dev Comp Immuno 6(3): 557-567.

20. Halpin K, Young PL, Field HE, Mackenzie JS (2000) Isolation of Hendra virus from pteropid bats: a natural reservoir of Hendra virus. The Journal of general virology. 81(Pt 8): 1927-1932.

21. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, et al. (2005) Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci USA 102(39): 14040-14045.

22. Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, et al. (2005) Fruit bats as reservoirs of Ebola virus. Nature 438(7068): 575-576.

23. Zhou P, Tachedjian M, Wynne JW, Boyd V, Cui J, et al. (2016) Contraction of the type I IFN locus and unusual constitutive expression of IFN-alpha in bats. Proc Natl Acad Sci USA 113(10): 2696-2701.

24. Wynne JW, Shiell BJ, Marsh GA, Boyd V, Harper JA, et al. (2014) Proteomics informed by transcriptomics reveals Hendra virus sensitizes bat cells to TRAIL-mediated apoptosis. Genome Biol 15(11): 532.

25. Ahn M, Cui J, Irving AT, Wang LF (2016) Unique loss of the PYHIN gene family in bats amongst mammals: Implications for inflammasome sensing. Scientific reports 6: 21722.

26. Pavlovich SS, Lovett SP, Koroleva G, Guito JC, Arnold CE, et al. (2018) The Egyptian rousette genome reveals unexpected features of bat antiviral immunity. Cell 173(5): 1098-110.e18.

27. Stetson DB, Medzhitov R (2006) Type I interferons in host defense. Immunity 25(3): 373-381.

28. Johnson JS, Gentzsch M, Zhang L, Ribeiro CM, Kantor B, et al. (2011) AAV exploits subcellular stress associated with inflammation, endoplasmic reticulum expansion, and misfolded proteins in models of cystic fibrosis. PLoS pathogens 7(5): e1002053.

29. Trejo-de OA, Hernandez-Sancen P, Maldonado-Bernal C (2014) Relevance of single-nucleotide polymorphisms in human TLR genes to infectious and inflammatory diseases and cancer. Genes Immun 15(4): 199-209.

30. Reikine SN, Modis Y (2014) Pattern recognition and signaling mechanisms of RIG-I and MDA5. Front Immunol. 5: 342.

31. Li G, Fan Y, Lai Y, Han T, Li Z, et al. (2020) Coronavirus infections and immune responses. J Med Virol 92(4): 424-432.

32. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 588(7836): 1-4.

33. Wong C, Lam C, Wu A, Ip W, Lee N, et al. (2004) Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 136(1): 95-103.

34. Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA (2018) MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 104: 8-13.

35. Dandekar AA, Perlman S (2005) Immunopathogenesis of coronavirus infections: implications for SARS. Nat Rev Immunol 5(12): 917-927.

36. Zumla A, Hui DS, Perlman S (2015) Middle East respiratory syndrome. Lancet 386(9997): 995-1007.

37. Lambrecht BN, Neyt K, van Helden MJ (2015) The mucosal immune response to respiratory viruses. Mucosal Immunology 2: 1805-1815.

38. Brandtzaeg P (2010) Function of mucosa-associated lymphoid tissue in antibody formation. Immunol Invest 39(4-5): 303-355.

39. Nakanishi Y, Lu B, Gerard C, Iwasaki A (2009) CD8+ T lymphocyte mobilization to virus-infected tissue requires CD4+ T-cell help. Nature 462(7272): 510-513.

40. Mantis NJ, Rol N, Corthésy B (2011) Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol 4(6): 603-611.

41. Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, et al. (2006) Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 193(6): 792-795.

42. Liu WJ, Zhao M, Liu K, Xu K, Wong G, et al. (2017) T-cell immunity of SARS-CoV: Implications for vaccine development against MERS-CoV. Antiviral Res 137: 82-92.

43. Blackwell JM, Jamieson SE, Burgner D (2009) HLA and infectious diseases. Clin Microbiol Rev 22(2): 370-385.

44. Matzaraki V, Kumar V, Wijmenga C, Zhernakova A (2017) The MHC locus and genetic susceptibility to autoimmune and infectious diseases. Genome biology 18(1): 76.

45. Dutta M, Dutta P, Medhi S, Borkakoty B, Biswas D (2018) Polymorphism of HLA class I and class II alleles in influenza A (H1N1) pdm09 virus infected population of Assam, Northeast India. J Med virol 90(5): 854-860.

46. Ohno S, Kohyama S, Taneichi M, Moriya O, Hayashi H, et al. (2009) Synthetic peptides coupled to the surface of liposomes effectively induce SARS coronavirus-specific cytotoxic T lymphocytes and viral clearance in HLA-A* 0201 transgenic mice. Vaccine 27(29): 3912-3920.

47. Li Q, Guan X, Wu P, Wang X, Zhou L, et al. (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England Journal of Medicine 382: 1199-1207.

48. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J (2020) The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 27(2): 021.

49. Abdulamir A, Hafidh R (2020) The possible immunological pathways for the variable immunopathogenesis of Covid-19 infections among healthy adults, elderly and children. Electron J Gen Med 17(4): em202. 2020.

50. Fujihashi K, Kiyono H (2009) Mucosal immunosenescence: new developments and vaccines to control infectious diseases. Trends in immunology 30(7): 334-343.

51. Salvioli S, Capri M, Valensin S, Tieri P, Monti D, et al. (2006) Inflamm-aging, cytokines and aging: state of the art, new hypotheses on the role of mitochondria and new perspectives from systems biology. Curr pharm des 12(24): 3161-3171.

52. Adkins B, Leclerc C, Marshall-Clarke S (2004) Neonatal adaptive immunity comes of age. Nat Rev Immunol 4(7): 553-564.

53. Björkstén B (1999) The intrauterine and postnatal environments. Journal of allergy and clinical immunology. 104(6): 1119-1127.

54. Clay CC, Reader JR, Gerriets JE, Wang TT, Harrod KS, et al. (2014) Enhanced viral replication and modulated innate immune responses in infant airway epithelium following H1N1 infection. Journal of virology. 88(13): 7412-7425.

55. Oshansky CM, Gartland AJ, Wong SS, Jeevan T, Wang D, et al. (2014) Mucosal immune responses predict clinical outcomes during influenza infection independently of age and viral load. Am J Respir Crit Care Med 189(4): 449-462.

56. Belderbos M, Van Bleek G, Levy O, Blanken M, Schuijff L, et al. (2009) Skewed pattern of Toll-like receptor 4-mediated cytokine production in human neonatal blood: low LPS-induced IL-12p70 and high IL-10 persist throughout the first month of life. Clinical immunology 133(2): 228-237.

57. Siegrist CA, Aspinall R (2009) B-cell responses to vaccination at the extremes of age. Nat Rev Immunol 9(3): 185-194.

58. Zimmermann P, Perrett KP, Messina NL, Donath S, Ritz N, et al. (2019) The effect of maternal immunisation during pregnancy on infant vaccine responses. E Clinical Medicine 13: 21-30.

59. Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 46(5):1-3.

60. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ (2020) The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 55(5): 105954.

61. Nagai A, Matsumiya H, Hayashi M, Yasui S, Okamoto H, et al. (1994) Effects of nicotinamide and niacin on bleomycin-induced acute injury and subsequent fibrosis in hamster lungs. Exp Lung Res 20(4): 263-281.

62. Wang Y, Chen X, Cao W, Shi Y (2014) Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nat Immunol 15(11): 1009-1016.

63. Velavan TP, Meyer CG (2020) The COVID-19 epidemic. Trop Med Int Health 25(3): 278-280.

64. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y (2020) Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv.

65. Wardhana DE, Sultana A, Mandang V, Jim E (2011) The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper

respiratory tract infection in the elderly. Acta Med Indones. 43(3): 185-190.

66. Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, et al. (2014) Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. J Innate Immun 6(2): 152-158.

67. Vetskova EK, Muhtarova MN, Avramov TI, Stefanova TR, Chalakov IJ, et al. (2013) Immunomodulatory effects of BCG in patients with recurrent respiratory papillomatosis. Folia Med 55(1): 49-54.

68. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G (2016) Trained immunity: a program of innate immune memory in health and disease. Science 352(6284): aaf1098.

69. WHO (2020) Bacille calmette-guérin (BCG) vaccination and COVID-19: scientific brief.