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Original article

The Protective Mechanism Against COVID-19, Antibody vs Cellular Immunity: An Extensive Review

Khalid Shrwani [1], Nabil Dhayhi [2], Waleed Mahallawi [3], Alaa Sherwani [4], Mohammed Badedi [5], Saeed Aldossari [6], Abdulrahman Muhajir [7], Zeinab Hassan [8], Nouf Sherwani [9], Tarig Karar [10, 11], Eyad Gadour [12, 13]

[1]Department of Clinical Infection, Microbiology and Immunology, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK. 2- Public Health Authority, Saudi Center for Disease Prevention and Control (SCDC), B.O. Box 716 Jazan 45142, KSA.
[2]Department of Pediatrics, King Fahad Central Hospital, Ministry of Health, Jazan region, KSA.
[3]Medical Laboratory Technology Department, College of Applied Medical Sciences, Taibah University, Madinah, KSA.
[4]Department of Pediatrics, Abu-Arish General Hospital, Ministry of Health, Jazan region, KSA.
[5]Administration of Research & Studies, Jazan Health Affairs, Ministry of Health, Jazan region, KSA.
[6]Medical Laboratory Technology Department, College of Applied Medical Sciences, King Saud University, Riyadh, KSA.
[7]Department of Microbiology, Jazan regional Laboratory, Ministry of Health, Jazan region, KSA.
[8]Department of Medicine, Stockport Hospital NHS Foundation Trust, Manchester-UK.
[9]Department of Surgery, Mohammed bin Nasser Hospital, Ministry of Health, Jazan region, KSA.
[10]Clinical Laboratory Science Department, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences, Al Ahsa- Saudi Arebia,
[11]King Abdullah International Medical Research Centre, Al Ahsa- Saudi Arabia.
[12]Department of Gastroenterology and Hepatology, King Abdulaziz National Guard Hospital, Ahsa-KSA.
[13]Department of Internal Medicine, Faculty of Medicine, Zamzam University College, Khartoum-Sudan

*Corresponding author: Dr Eyad Gadour; FACP FRCP; *eyadgadour@doctors.org.uk*

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Abstract

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a significant threat to the world, causing a respiratory illness with a wide range of symptoms and affecting people of all sexes and age groups. Although the innate immune response to SARS-CoV-2 is not entirely understood, recent findings suggest that a high number of innate immune cells and inflammatory cytokines can help in fighting the virus. However, an excessive expression of cytokines can lead to a cytokine storm, resulting in a severe disease state with high morbidity and mortality. The coordinated actions of the innate and adaptive immune responses are responsible for eliminating virus-infected cells and inhibiting reinfection. The actual role of T-cell immunity and antibody responses is unclear, and further research is necessary to gain insights into the nature of immune protection. The SARS-CoV-2 S protein is considered a sensitive and useful protein that can be targeted by antibodies and T cells, providing significant biological targets for finding effective vaccines and treatments. Despite challenges in developing effective vaccines, the small number of reinfections suggests that a primary infection may offer some protection during subsequent exposure to the same virus. A deeper understanding of the vital role of B and T cells in COVID-19 may help in managing, controlling, and halting this new pandemic.

Keywords: ***Antibody, cellular immunity, COVID-19***

Introduction

The coronavirus disease-2019 (COVID-19) pandemic has caused unprecedented global health, social, and economic challenges. As of April 2023, over 674 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, and more than 6.9 million people have died worldwide [1]. The rapid spread of this virus has necessitated the development of effective interventions and vaccines to control its transmission and mitigate its effects.

Immunological protective mechanisms against SARS-CoV-2 infection involve both innate and adaptive immune responses. The innate immune system is the first line of defense against viral infections. It provides immediate and nonspecific responses to

eliminate pathogens. It has several components, such as complement proteins, natural killer cells, dendritic cells, and macrophages, which work together to detect and eliminate invading viruses [2].

During SARS-CoV-2 infection, innate immune cells produce a range of proinflammatory cytokines and chemokines, including interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, and interferons (IFNs), to mount an early immune response [3]. Although these cytokines are essential for the activation of adaptive immunity, their dysregulated production can lead to an excessive inflammatory response, resulting in tissue damage and organ dysfunction, a phenomenon known as cytokine storm [4]. Adaptive immunity consists of humoral immunity and cellular immunity, representing the interdependent and complementary arms of the immune system [5]. Humoral immunity involves the production of virus-specific antibodies by B cells, which can neutralize viral particles, prevent their entry into host cells, and promote their clearance by phagocytic cells [6]. Conversely, cellular immunity involves the activation of T cells, which can recognize and eliminate the infected cells and prevent viral replication (**Fig. 1**) [7].

The levels of neutralizing antibodies and memory B cells were found to be correlated with the severity of COVID-19 and patient age [8,9]. Similarly, T-cell responses were shown to be crucial for the control of SARS-CoV-2 infection, and their dysfunction was associated with severe COVID-19 and mortality [10,11]. However, the role of humoral and cellular immunity in providing protective immunity against SARS-CoV-2 infection remains a subject of intense investigation and debate. Some studies have suggested that neutralizing antibodies are the primary mediators of protection against SARS-CoV-2, as they can prevent viral entry and can promote viral clearance [12]. Other studies have proposed that cellular immunity plays a more crucial role in controlling SARS-CoV-2 infection and preventing disease progression, as it can recognize and eliminate infected cells, even in the absence of neutralizing antibodies [13].

The timing, quality, and magnitude of the immune response, as well as the viral load and genetic variability of the virus, can influence the relative contribution of humoral and cellular immunity against SARS-CoV-2 [14]. Moreover, the emergence of new SARS-CoV-2 variants with mutations in the spike protein, the main target of neutralizing antibodies, has raised concerns regarding the efficacy of current vaccines and the durability of protective immunity [15].

Immunological defense mechanisms against SARS-CoV-2 infection

Innate immune responses

The immune system plays a crucial role in protecting the body from pathogens such as bacteria, viruses, and parasites [16,17]. The immune system is divided into innate immunity and adaptive immunity [18] (**Fig. 1**). Innate immunity is the first line of defense against pathogens and is essential in initiating the immune response. This response is nonspecific and does not rely on previous exposure to a specific pathogen [19]. The host immune system identifies the viral particles or its surface epitopes, activating both the innate and adaptive immune responses once the pathogen enters the target cells (**Fig. 2**). In general, cytokines play a major role in mediating the immune response to SARS-CoV-2 [20]. An interesting finding is the increased secretions of proinflammatory cytokines and chemokines, including TNF-α, monocyte chemoattractant protein-1 (MCP-1), IFN gamma-induced protein 10 (IP-10), and macrophage inflammatory protein-1-alpha (MIP-1A), during SARS-CoV-2 infection [21]. Another important finding was as follows: C-reactive protein, IL-6, and neutrophils were all detected in high rates with approximately 86%, 52%, and 38%, respectively, among 99 patients with COVID-19 in Wuhan [19,22].

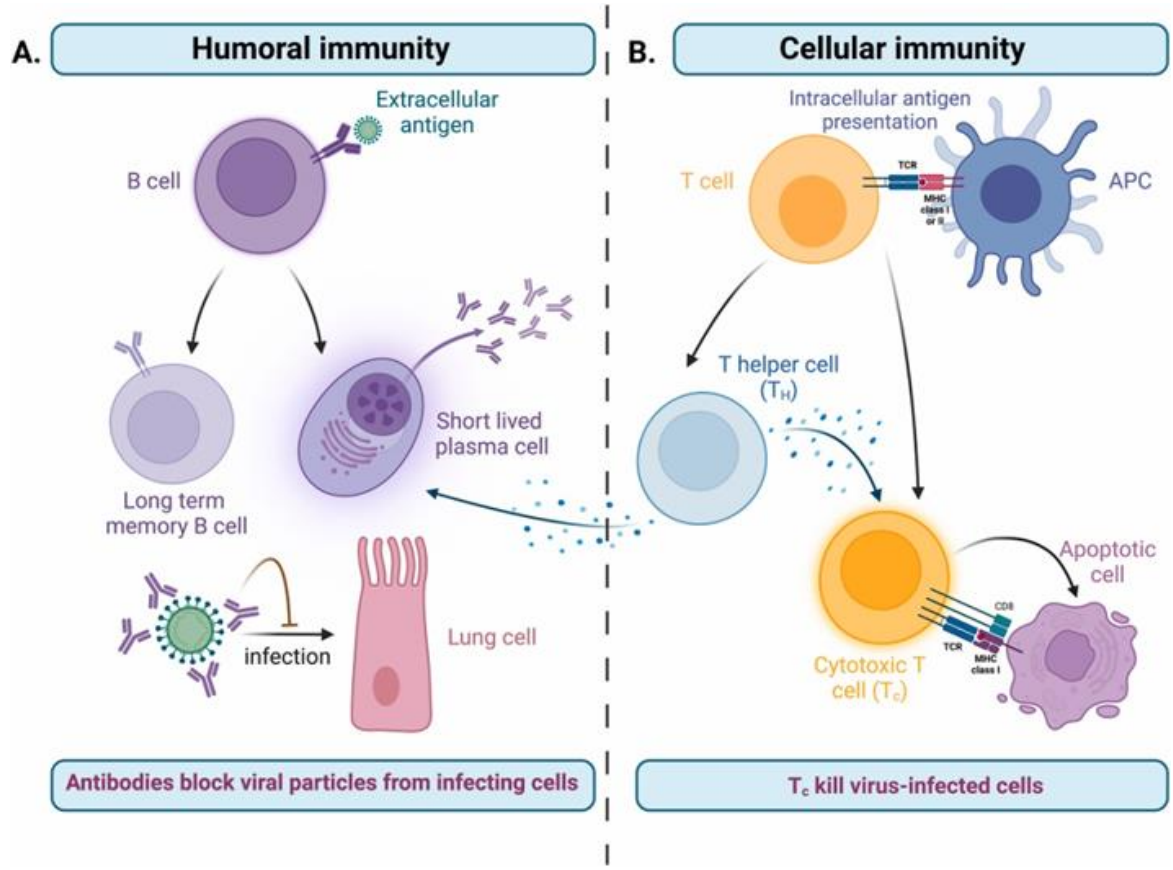

Fig. 1. The adaptive immune system has two main arms: A: the humoral response, which involves B cells producing antibodies to prevent infection, and B: the cellular response, which involves T cells identifying and killing infected cells. Both arms work together to provide immunity against pathogens. (Courtesy of Schwarz et al., 2022) [23]

The innate immune response consists of physical barriers, cellular components, and soluble factors that work together to recognize and eliminate pathogens. One of the primary physical barriers is the skin, which acts as a physical barrier against invading pathogens. In addition, the mucosal surfaces of the respiratory, gastrointestinal, and urogenital tracts are essential physical barriers. These surfaces produce mucus, which traps pathogens, and contain cilia, which move the mucus and any trapped pathogens out of the body [23,24].

Toll-like receptors (TLRs) are also an essential component of innate immunity. These receptors are expressed on immune cells and can recognize pathogen-associated molecular patterns that are unique to pathogens [25]. The activation of TLRs leads to the production of cytokines and chemokines, which recruit immune cells to the site of infection [19,25]. Subsequently, TRIF triggers NF-κB transcription factors and IRF-3 to stimulate TNF-β and IFN-α [19]. The type I IFN pathway is one of the key mechanisms that the innate immune system uses to combat viral infections. When a virus invades a host cell, it triggers the production of type I IFNs, which then bind to their receptors on nearby cells and initiate a cascade of signaling events [19]. This signaling cascade activates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) (JAK–STAT) pathways, leading to the migration of phosphorylated STAT-1 and 2, as well as tyrosine kinase-2 (TYK-2) and JAK-1 kinases, into the nucleus [19]. The upregulation of ISGs results in the suppression of viral replication and ultimately reduces disease severity [26-31]. Antigen-presenting cells (APCs) use MHC-1 receptors on the surface of CD4+ T-helper cells to present antigens of coronaviruses (CoVs) and activate T-helper type-1 (Th-1) cells by releasing IL-12 subunits, which are costimulatory molecules [19].

However, the excessive expression of chemokines and cytokines from immune effector cells can lead to hyperinflammation and acute respiratory distress syndrome (ARDS) [19,32-34]. In particular, chemokines CXCL-10, CXCL-9, CXCL-8, CCL-5, CCL-3, and CCL-2 and cytokines IL-33, IL-18, IL-12, IL-6, IL-1β, TNF-α, transforming growth factor beta (TGF-β), IFN-γ, and IFN-α are known to be involved in the pathogenesis of ARDS [19,32-34].

Pattern of cytokine expression post-SARS-CoV-2 infection

In SARS-CoV-2 infection, studies have shown high levels of several cytokines and chemokines, including vascular endothelial growth factor (VEGF), TNF-α, HGF, and MCP-1 [21,35-37]. High levels of VEGF have been detected in patients with COVID-19, particularly in those admitted to intensive care units (ICUs). TNF-α, which is crucial for regulating proinflammatory mechanisms, is also elevated in patients with COVID-19, particularly in severe cases [35]. HGF is secreted by damaged tissues, including pulmonary fibroblasts, and high levels have been detected in the serum samples of patients with COVID-19. MCP-1, a monocyte chemotactic molecule, is secreted by several cell types and plays an important role in the antiviral immune response [37]. High levels of MCP-1 have been detected in patients with COVID-19, particularly in those admitted to the ICU, and are linked to the pathogenesis of the virus [35].

IFN-γ is a type II IFN that is produced by various myelocyte and lymphocyte cells, including macrophages, monocytes, neutrophil granulocytes, dendritic cells, NKCs, B cells, FoxP3+ CD8 T cells, CD8+ T cells, Treg cells, and CD4+ T cells [37-39]. It has a crucial role in several immunological functions, including APC promotion, macrophage activation, and signal transduction, and acts as an antivirus and antibacterial. A study found high levels of IFN-γ in the serum samples of patients with COVID-19, particularly motivated by Th-1 and Th-2 cells [40].

IP-10, an IFN-γ-induced chemokine, is secreted by various cells, including dendritic cells, neutrophils, fibroblasts, endothelial cells, keratinocytes, hepatocytes, and astrocytes [36]. It regulates the immune system responses by activating and recruiting monocytes, NKCs, and T cells, following its binding to CXCR-3 [38]. In addition, the overproduction of IP-10 accelerates disease progression [21]. Patients with severe COVID-19 have also shown a significant increase in IP-10 expression, which is linked to disease progression and high mortality rate, along with the expression of IL-1Ra and MCP-3 [40].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a heterodimeric complex that can bind to Granulocyte colony-stimulating factor (G-CSF) and homodimerize. It is mainly produced by the endothelium, fibroblasts, epithelial cells, hematopoietic cells, and stromal cells and plays a crucial role in the inflammatory process by stimulating the production and activation of various immune cells. High levels of G-CSF have been detected in patients with severe COVID-19 and are associated with multiorgan failure and lung atrophy. M-CSF, also known as CSF-1, plays a major role in regulating the development and differentiation of hematopoietic cells, mainly monocytes, macrophages, and osteoclasts [21]. High levels of M-CSF have been detected in patients with COVID-19 and are directly linked to lung failure and disease severity [37].

IL-1, produced by activated macrophages and monocytes, contributes to the immune system's response to inhibit infection [40]. High levels of IL-1Ra and IL-1α have been detected in patients with severe COVID-19 and are closely linked to lung damage, reduced pulmonary function, and an increased mortality rate [35]. IL-2 is crucial for maintaining self-tolerance, controlling the immune system, and inhibiting autoimmune diseases [36]. High levels of IL-2 and its receptor IL-2R have been detected in patients with severe COVID-19 [38]. IL-4 has anti-inflammatory properties and plays an important role in regulating immune cells. High levels of IL-4 have been detected in patients with COVID-19 and severe respiratory symptoms due to cytokine storm [35]. In addition, IL-6 is produced by various cells and has multiple effects on the body, including regulating immune responses, inflammation, and blood cell formation [21,22,35]. Studies have found that IL-6 levels are higher in severe COVID-19 cases than in mild cases and other viral infections such as severe acute respiratory syndrome and Middle East respiratory syndrome [41]. High IL-7 levels have been found in patients with COVID-19 and are directly associated with disease severity [38]. IL-10 can block proinflammatory cytokines and can inhibit the immune response [42]. However, it can also stimulate the immune system in certain situations. High IL-10 levels have been found in severe COVID-19 cases and may serve as a predictive indicator of disease progression [22].

IL-12 and IL-13 are involved in inducing tissue responses to infections and be directly related to the viral load in patients with COVID-19 [22,35]. IL-17 level, another proinflammatory cytokine, is elevated in patients with COVID-19 with severe symptoms as a part of the cytokine storm mechanism [35].

Adaptive immune responses

APCs contribute to the production and expression of proinflammatory cytokines by activating NF-κB signaling pathways [19,43]. During SARS-CoV-2 infection, the release of proinflammatory cytokines, particularly IL-17, is elevated, leading to the migration of monocytes and neutrophils to infection sites and the stimulation of proinflammatory chemokines such as MCP-1, TNF-β, IL-21, IL-8, IL-6, and IL-1 [19,23,24, 45,46]. The activation of Th-1 cells also triggers the activation of CD8+ cytotoxic T cells, which target and eliminate SARS-CoV-2-infected cells, and CD4+ T-helper cells enhance T-cell-dependent activation of B cells for stimulating humoral immunity and inducing antigen-specific antibody production [23,44,45]. Following SARS-CoV-2 infection, unique patterns of IgG and IgM antibodies are produced, with IgM levels increasing and remaining high for up to 12 weeks and IgG levels persisting for long periods [19,46]. Exposure to CoVs can also lead to the formation of cell-mediated immunity, specifically CD4+

T cells and CD8+ memory T cells that can persist for up to 4 years and can neutralize the S proteins during the first exposure to the antigen [47-49]. The development of potential CoV vaccines is promising, given the ability to induce long-lasting immunity in humans, particularly in the context of the current SARS-CoV-2 pandemic [47].

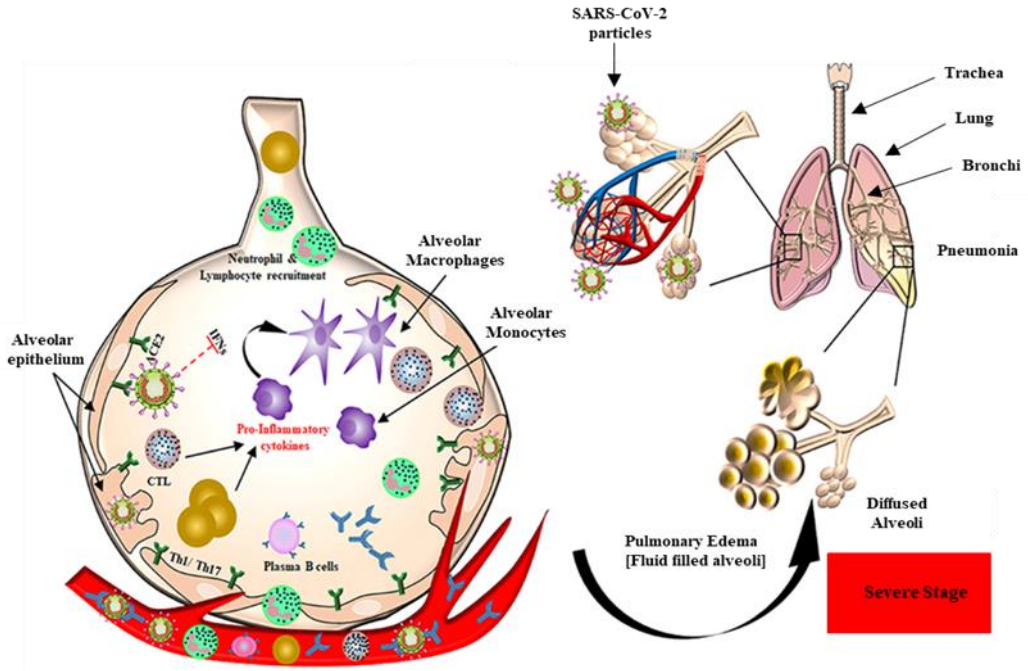

Fig. 1: SARS-CoV-2 targets cells of the respiratory system via ACE2 receptors and evades IFN antiviral responses. The presence of the virus leads to proinflammatory cytokine production, resulting in immune cell infiltration and severe immune reactions causing pneumonia and pulmonary edema. CD4+ T-helper cells and CD8+ effector T cells are recruited to the site of infection to destroy virus-infected cells in the lungs. B cells/plasma cells are activated to generate anti-SARS-CoV-2-specific antibodies to disrupt the viral distribution and offer systemic humoral immune responses in various organs (Adapted from Shah et al. 2020) [32].

A reduction in T-lymphocyte levels has been linked to increased apoptosis mechanisms and poor outcomes in patients with COVID-19 [50].

Antibody responses to SARS-CoV-2 infection

In response to viral infections, B and T-lymphocyte cells work together to create lasting immune responses [51]. During SARS-CoV-2 infection, adaptive immune responses are needed to prevent disease progression to its severe stages [52]. The presence of specific immunoglobulin antibodies, such as IgA, IgM, and IgG, contributes to a better outcome for infected individuals [53-57]. These antibodies can neutralize the viral particles by binding to the S glycoprotein and other membrane proteins [58]. Early and rapid antibody responses can be achieved by either naïve B cells or memory B cells that have been informed by prior human CoVs [56]. The balance between these two types of immune cells may have a positive effect on the clinical consequences of the viral infection [58].

When do humoral immune responses appear and how long do they last?

Following SARS-CoV-2 infection, those infected show humoral immune responses between day 10 and day 21 postinfection. IgG and IgM antibodies develop between 6 and 15 days after illness onset [59]. Within the first week from symptom onset, antibody levels were detected in <40% of patients with COVID-19 [58,60,61]. Patients with detectable antibodies increased to 100% (total antibodies) at day 15 postsymptom onset. IgM and IgG antibody levels among patients with COVID-19 may persist for more than 7 weeks in 80% of the reported cases [62]. On the basis of the dynamics of the antibodies and clinical-onset serial intervals of COVID-19, the duration of protective immunity against infection may remain between 6 and 12 months [63,64]. The effective implementation of convalescent plasma in patients with severe COVID-19 supports the role of antibodies in viral eradication [65]. The detection of antibodies and correlates of protection to SARS-CoV-2 does not provide a protective immune response, as they have not yet been studied in detail [66,67].

Longitudinal observation and decline in neutralizing antibody responses

Studies have shown a significant decline in the levels of neutralizing antibodies and anti-SARS-CoV-2-specific IgG antibodies in patients with both symptomatic and asymptomatic COVID-19 2–3 months after symptom onset [68]. Some patients have been found to provide low levels of neutralizing antibodies within 3 months of recovery [69]. Even after releasing patients with asymptomatic infection from isolation, approximately 40% of them tested negative for anti-SARS-CoV-2-specific IgG antibodies 8 weeks later [70]. The differential susceptibility of COVID-19 between children, adults, and older people does not reflect the quantitative differences in antibody titers [65]. A correlation was found between antibody titers and cumulative viral load. Individuals with very mild exposure may display undetectable antibody responses [70].

T-cell immune response to SARS-CoV-2 infection

Human cells infected by SARS-CoV-2 can present epitopes from viral proteins through MHC class I antigen-presenting molecules on the cell surface, leading to the activation of CD4+ and CD8+ T cells and induction of humoral and cell-mediated immune responses. Four subsets of T-lymphocyte cells, namely, CD4+ T-helper cells, CD8+ T cells, T-helper 17 (Th-17), and regulatory T cells (Tregs), are involved in inducing effective immune responses to SARS-CoV-2 infection [71,79].

Mechanisms of T-lymphocyte cell responses

Infected human cells can present epitopes of viral proteins through MHC class I molecules, inducing CD4+ and CD8+ T-cell responses that stimulate humoral and cell-mediated immune responses. CD4+ T-helper cells enhance cellular immune responses and stimulate B lymphocytes to secrete neutralizing antibodies, and CD8+ T cells are responsible for the direct killing of infected cells [72-78]. Th-17 and Tregs control infection and prevent tissue destruction [79,80]. All T- and B-cell subtypes develop immunological memory cells after a primary encounter with a pathogen, providing effective immune responses upon encountering the same or closely related pathogens [81]. Characterization of T-lymphocyte cells against SARS-CoV-2 S protein has been established for designing effective vaccines and understanding long-term immune responses [82]. Both mild and severe COVID-19 cases display a decreased absolute number of T lymphocytes, chiefly CD4+ T cells and CD8+ T cells, with severe cases showing lowered expression of IFN-γ by CD4+ T cells [82]. The independent prediction of ineffective treatment outcomes was identified following post-treatment with a decrease in B cells and CD8+ T cells and an increase in CD4+/CD8+ T-cell ratio [83].

Presence of SARS-CoV-2-specific T cells pre- and postinfection

T cells play a crucial role in combating SARS-CoV-2 infection both during acute illness and in recovered individuals. Specific CD4+ T-helper cells and killer CD8+ T cells have been detected in patients with and without humoral-mediated immunity, including those who repeatedly tested negative for the virus [56]. T-cell memory responses are also important for long-lasting cell immunity and can contribute to the production of virus-neutralizing antibodies in the blood and at mucosal infection sites [84]. Neutralizing antibody titers correlated with antiviral T-cell immune responses. However, data available on cell-mediated immunity, particularly T-cell immune responses, in human CoV studies are still limited [56].

Can pre-existing cross-reactive immune responses provide effective protection against SARS-CoV-2 infection?

A study showed that T cells play a vital role in combating SARS-CoV-2 infection, even in individuals without developed humoral-mediated immunity or a history of virus exposure [58]. Memory T cells also contribute to long-lasting immunity and can enhance the production of virus-neutralizing antibodies [82]. The duration of the effective immune responses to SARS-CoV-2 infection is still unclear, and pre-existing immunological memory cells from other human coronaviruses may complicate the understanding of the correlation with SARS-CoV-2 infection [58]. However, evidence suggests that pre-existing cross-reactive T-cell memory against common cold CoVs can provide protective immune responses against SARS-CoV-2. Further research is needed to determine the significance of these cross-reactive responses in unexposed healthy and infected individuals. The absence of pre-existing immunity is believed to be a contributing factor to the rapid outbreak and transmission of SARS-CoV-2 [83].

What causes T-cell exhaustion in cases of persistent SARS-CoV-2 infection?

The dysfunction of T cells during COVID-19 is characterized by reduction and exhaustion, which may be induced by cytokines such as IL-10, TNF-α, and IL-6 [51,52]. Low T-cell numbers and exhaustion increase the likelihood of severe disease progression and susceptibility to secondary infections [61]. Further research is needed to understand the role of T cells in COVID-19 progression and recovery, including the longitudinal course of SARS-CoV-2-specific T cells in recovered patients, the role of Treg cells in cytokine storm syndrome, and the relationship between anti-SARS-CoV-2 IgG antibodies and disease severity [83]. In addition, the mechanisms for removing SARS-CoV-2 infectious particles remain incomplete [62].

Conclusion and future research direction

The emergence of SARS-CoV-2 has led to a global threat with a wide range of clinical symptoms. Innate and adaptive immune responses are essential for eliminating the virus; however, excessive cytokine expression can lead to severe pathology. The reduction in the number of CD4+ and CD8+ T cells in severe cases is due to an increased apoptosis process. The antibody immune response can last for 6–12 months, with the SARS-CoV-2 S protein being a useful protein indicator for vaccines and treatments. Vaccine development requires essential factors such as safety, stability, and durability. Although reinfection has been detected, primary infection with SARS-CoV-2 may provide some protection. Further research is needed to understand T-cell immunity and antibody responses. B and T cells may play a crucial role in managing and halting this pandemic.

Ethics approval and consent to participate

Not applicable.

List of abbreviations

The abbreviations are listed in the main article.

Data Availability

All data collected are available and could be requested from the corresponding author.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

The individual contributions of authors tis equal. All authors read and approved the final manuscript."

References

[1] Chen, Y., Liu, Q. & Guo, D. (2020). Emerging coronaviruses: Genome structure, replication, and pathogenesis. Journal of Medical Virology, 92, 418–423.

[2] Hafeez, A., Ahmad, S., Siddqui, S.A., Ahmad, M. & Mishra, S. (2019). A review of COVID-19 (coronavirus Disease-2019) diagnosis, treatments and prevention. Ejmo. Apr, 4, 116–125.

[3] Centers for Disease Control and Prevention (CDC). (2020). Coronavirus [Online]. Available at: https://www.cdc.gov/coronavirus/types.html. Accessed 5/7/2022.

[4] World Health Organization (WHO). (2020). Q&A on coronaviruses (COVID-19) [Online]. Available at: https://www.who.int/news-room/q-a-detail/q-a-coronaviruses. Accessed 5/7/2022.

[5] Li, H., Liu, S.M., Yu, X.H., Tang, S.L. & Tang, C.K. (2020). Coronavirus disease 2019 (COVID-19): Current

status and future perspectives. International Journal of Antimicrobial Agents, 55, 105951

[6] Ahn, D.G., Shin, H.J., Kim, M.H., Lee, S., Kim, H.S., Myoung, J., Kim, B.T. & Kim, S.J. (2020). Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). Journal of Microbiology and Biotechnology, 30, 313–324.

[7] Feng, S., Shen, C., Xia, N., Song, W., Fan, M. & Cowling, B.J. (2020). Rational use of face masks in the COVID-19 pandemic. Lancet. Respiratory Medicine, 8, 434–436.

[8] Bi, Q., Wu, Y., Mei, S., Ye, C., Zou, X., Zhang, Z., Liu, X., Wei, L., Truelove, S.A., Zhang, T., Gao, W., Cheng, C., Tang, X., Wu, X., Wu, Y., Sun, B., Huang, S., Sun, Y., Zhang, J., Ma, T., Lessler, J. & Feng, T. (2020). Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: A retrospective cohort study. Lancet. Infectious Diseases, 20, 911–919.

[9] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (2020). The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology, 5, 536–544.

[10] Centers for Disease Control and Prevention (CDC). (2020). About 2019 novel coronavirus (2019-nCoV) [Online] Available at: [Accessed 5 7 2022].

[11] Hemida, M.G. & Ba Abduallah, M.M. (2020). The SARS-CoV-2 outbreak from a one health perspective. One Health, 10, 100127.

[12] Khailany, R.A., Safdar, M. & Ozaslan, M. (2020). Genomic characterization of a novel SARS-CoV-2. Gene Reports, 19, 100682.

[13] Singhal, T. (2020). A review of coronavirus disease-2019 (COVID-19). Indian Journal of Pediatrics, 87, 281–286.

[14] Conti, P. & Younes, A. (2020). Coronavirus COV-19/SARS-CoV-2 affects women less than men: Clinical response to viral infection. Journal of Biological Regulators and Homeostatic Agents, 34, 339–343.

[15] Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., Zimmer, T., Thiel, V., Janke, C., Guggemos, W., Seilmaier, M., Drosten, C., Vollmar, P., Zwirglmaier, K., Zange, S., Wölfel, R. & Hoelscher, M. (2020). Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. New England Journal of Medicine, 382, 970–971.

[16] Kampf, G., Todt, D., Pfaender, S. & Steinmann, E. (2020). Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. Journal of Hospital Infection, 104, 246–251.

[17] Li, J.O., Lam, D.S.C., Chen, Y. & Ting, D.S.W. (2020). Novel coronavirus disease 2019 (COVID-19): The importance of recognising possible early ocular manifestation and using protective eyewear. British Journal of Ophthalmology, 104, 297–298.

[18] Yuen, K.S., Ye, Z.W., Fung, S.Y., Chan, C.P. & Jin, D.Y. (2020). SARS-CoV-2 and COVID-19: The most important research questions. Cell and Bioscience, 10, 40.

[19] Indwiani Astuti, Y. (2020). Severe acute respiratory syndrome coronavirus, 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes & Metabolic Syndrome.

[20] Yi, Y., Lagniton, P.N.P., Ye, S., Li, E. & Xu, R.H. (2020). COVID-19: What has been learned and to be learned about the novel coronavirus disease. International Journal of Biological Sciences, 16, 1753–1766.

[21] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J. & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 395, 497–506.

[22] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X. & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet, 395, 507–513.

[23] Schwarz, M., Mzoughi, S., Lozano-Ojalvo, D., Tan, A.T., Bertoletti, A. & Guccione, E. (2022). T cell immunity is key to the pandemic endgame: How to measure and monitor it. Current Research in Immunology, 3, 23. - Rabi, F., Al Zoubi, M., Kasasbeh, G., Salameh, D., and Al-Nasser, A. (2020). SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens, 9(3), p. 231.

[24] Li, G., Fan, Y., Lai, Y., Han, T., Li, Z., Zhou, P., Pan, P., Wang, W., Hu, D., Liu, X., Zhang, Q. & Wu, J. (2020). Coronavirus infections and immune responses. Journal of Medical Virology, 92, 424–432.

[25] Park, A. & Iwasaki, A. (2020). Type I and Type III interferons–induction, signalling, evasion, and application to combat COVID-19. Cell Host and Microbe, 27, 870–878.

[26] Mantlo, E., Bukreyeva, N., Maruyama, J., Paessler, S. & Huang, C. (2020). Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Research, 179, 104811.

[27] Onofrio, L., Caraglia, M., Facchini, G., Margherita, V., Placido, S. & Buonerba, C. (2020). Toll-like receptors and COVID-19: A two-faced story with an exciting ending. Future Science OA, 6, FSO605.

[28] Hardy, M. (2004). McGETTRICK, A, and O'Neill, L. Transcriptional Regulation of the Human TRIF (TIR domain-containing adaptor protein inducing interferon beta) gene. Biochemical Journal, 380, 83–93.

[29] Steen, H.C. & Gamero, A.M. (2013). STAT2 phosphorylation and signaling. JAK-STAT, 2, e25790.

[30] Piao, W., Ru, L.W., Piepenbrink, K.H., Sundberg, E.J., Vogel, S.N. & Toshchakov, V.Y. (2013). Recruitment of TLR adapter TRIF to TLR4 signaling complex is mediated by the second helical region of TRIF TIR domain. Proceedings of the National Academy of Sciences of the United States of America, 110, 19036–19041.

[31] Prompetchara, E., Ketloy, C. & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific Journal of Allergy and Immunology, 38, 1–9.

[32] Shah, V.K., Firmal, P., Alam, A., Ganguly, D. & Chattopadhyay, S. (2020). Overview of immune response during SARS-CoV-2 infection: Lessons from the past. Frontiers in Immunology, 11, 1949.

[33] Chen, J., Lau, Y.F., Lamirande, E.W., Paddock, C.D., Bartlett, J.H., Zaki, S.R. & 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, 1289–1301.

[34] Bartee, E. & McFadden, G. (2013). Cytokine synergy: An underappreciated contributor to innate anti-viral immunity. Cytokine, 63, 237–240.

[35] Costela-Ruiz, V.J., Illescas-Montes, R., Puerta-Puerta, J.M., Ruiz, C. & Melguizo-Rodríguez, L. (2020). SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine and Growth Factor Reviews, 54, 62–75.

[36] Liu, Y., Zhang, C., Huang, F., Yang, Y., Wang, F., Yuan, J., Zhang, Z., Qin, Y., Li, X., Zhao, D. & Li, S. (2020). Novel Coronavirus (2019-nCoV) Infections Trigger an Exaggerated Cytokine Response Aggravating Lung Injury, Vol. 2020.

[37] Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., Chen, L., Li, M., Liu, Y., Wang, G., Yuan, Z., Feng, Z., Zhang, Y., Wu, Y. & Chen, Y. (2020). Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Frontiers in Immunology, 11, 827.

[38] Sun, D., Li, H., Lu, X., Xiao, H., Ren, J., Zhang, F. & Liu, Z. (2020). Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: A single center's observational study. World Journal of Pediatrics, 16, 251–259.

[39] Lin, L., Lu, L., Cao, W. & Li, T. (2020). Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerging Microbes and Infections, 9, 727–732.

[40] Yang, Y., Shen, C., Li, J., Yuan, J., Yang, M., Wang, F., Li, G., Li, Y., Xing, L., Peng, L. & Wei, J. (2020). Exuberant Elevation of IP-10, MCP-3 and IL-1RA During SARS-CoV-2 Infection Is Associated with Disease Severity and Fatal Outcome. MedRxiv.

[41] Min, C., Cheon, S., Ha, N.Y., Sohn, K., Kim, Y., Aigerim, A., Shin, H., Choi, J., Inn, K., Kim, J. & Moon, J. (2016). Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Scientific Reports, 6, 1–12.

[42] Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., Qi, Y., Sun, R., Tian, Z., Xu, X. & Wei, H. (2020). Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+ CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. bioRxiv.

[43] Wong, C.K., Lam, C.W., Wu, A.K., Ip, W.K., Lee, N.L., Chan, I.H., Lit, L.C., Hui, D.S., Chan, M.H., Chung, S.S. & Sung, J.J. (2004). Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clinical and Experimental Immunology, 136, 95–103.

[44] Akhmerov, A. & Marbán, E. (2020) COVID-19 and the heart. Circulation Research, 126, 1443–1455.

[45] Murphy, K., Travers, P. & Walport, M. (2008). Janeway's im Munobiology, Vol. 15. Garland Science. Taylor & Francis Group, LLC, pp. 655–708.

[46] Zumla, A., Hui, D.S., Azhar, E.I., Memish, Z.A. & Maeurer, M. (2020). Reducing mortality from 2019-nCoV: Host-directed therapies should be an option. Lancet, 395, e35–e36.

[47] Li, X., Geng, M., Peng, Y., Meng, L., and Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. Journal of Pharmaceutical Analysis.

[48] Fan, Y.Y., Huang, Z.T., Li, L., Wu, M.H., Yu, T., Koup, R.A., Bailer, R.T. & Wu, C.Y. (2009). Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. Archives of Virology, 154, 1093–1099.

[49] Tang, F., Quan, Y., Xin, Z.T., Wrammert, J., Ma, M.J., Lv, H., Wang, T.B., Yang, H., Richardus, J.H., Liu, W. & Cao, W.C. (2011). Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: A six-year follow-up study. Journal of Immunology, 186, 7264–7268.

[50] O'Connell, P. & Aldhamen, Y.A. (2020). Systemic innate and adaptive immune responses to SARS-CoV-2 as it relates to other coronaviruses. Human Vaccines and Immunotherapeutics, 16, 2980–2991.

[51] Wang, F., Nie, J., Wang, H., Zhao, Q., Xiong, Y., Deng, L., Song, S., Ma, Z., Mo, P. & Zhang, Y. (2020). Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. Journal of Infectious Diseases, 221, 1762–1769.

[52] Zhang, B., Zhou, X., Zhu, C., Feng, F., Qiu, Y., Feng, J., Jia, Q., Song, Q., Zhu, B. & Wang, J. (2020). Immune Phenotyping Based on Neutrophilto-Lymphocyte Ratio and IgG Predicts Disease Severity and Outcome for Patients with COVID-19. medRxiv.

[53] Shurin, M.R., Morris, A., Wells, A. & Wheeler, S.E. (2020). Assessing immune response to SARS-CoV-2 infection. ImmunoTargets and Therapy, 9, 111–114.

[54] Cunningham, A.C., Goh, H.P. & Koh, D. (2020). Treatment of COVID-19: Old tricks for new challenges. Critical Care, 24, 91.

[55] Thevarajan, I., Nguyen, T.H.O., Koutsakos, M., Druce, J., Caly, L., van de Sandt, C.E., Jia, X., Nicholson, S., Catton, M., Cowie, B., Tong, S.Y.C., Lewin, S.R. & Kedzierska, K. (2020). Breadth of concomitant immune responses prior to patient recovery: A case report of non-severe COVID-19. Nature Medicine, 26, 453–455.

[56] Sewell, H.F., Agius, R.M., Stewart, M. & Kendrick, D. (2020). Cellular immune responses to Covid-19. BMJ, 370, m3018.

[57] Walls, A.C., Park, Y., Tortorici, M.A., Wall, A., McGuire, A.T. & Veesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell, 181, 281–292.e6.

[58] Beretta, A., Cranage, M. & Zipeto, D. (2020). Is cross-reactive immunity triggering COVID-19 immunopathogenesis? Frontiers in Immunology, 11, 567710.

[59] Eurobean Cntr. for Disease Control and Prevention (ECDC). (2020). Immune responses and immunity to SARS-CoV-2 [Online]. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/immune-responses. Accessed 5/7/2022.

[60] Woelfel, R., Corman, V., Guggemos, W., Seilmaier, M., Zange, S., Mueller, M. & Bleicker, T. (2020). Clinical Presentation and Virological Assessment of Hospitalized Cases of Coronavirus Disease 2019 in a Travel-Associated Transmission Cluster. MedRxiv.

[61] Zhao, J., Yuan, Q., Wang, H., Liu, W., Liao, X., Su, Y. & Qian, S. (2020). Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clinical Infectious Diseases.

[62] Long, Q., Liu, B., Deng, H.J., Wu, G., Deng, K., Chen, Y. & Wang, D. (2020). Antibody responses to SARS-CoV-2 in patients with COVID-19. Nature Medicine, 1–4.

[63] Liu, W., Liu, L., Kou, G. & Zheng, Y. (2020). Evaluation of Nucleocapsid and Spike Protein-Based ELISAs for Detecting Antibodies Against SARS-CoV-2. Medxriv.

[64] Long, Q., Deng, H., Chen, J., Hu, J., Liu, B., Liao, P. & Gong, F. (2020). Antibody responses to SARS-CoV-2. In: COVID-19 Patients: The Perspective Application of Serological Tests in Clinical Practice. medRxiv.

[65] Wan, W., Lim, S. & Seng, E. (2020). Cross-Reaction of Sera from COVID-19 Patients with SARS-CoV Assays. medRxiv.

[66] Kellam, P. & Barclay, W. (2020). The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. Journal of General Virology, 101, 791–797.

[67] Xiao, A.T., Gao, C. & Zhang, S. (2020). Profile of specific antibodies to SARS-CoV-2: The first report. Journal of Infection, 81, 147–178.
[68] Zeng, H., Xu, C., Fan, J., Tang, Y., Deng, Q., Zhang, W. & Long, X. (2020). Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA, 323, 1848–1849.
[69] Wu, L.P., Wang, N.C., Chang, Y.H., Tian, X.Y., Na, D.Y., Zhang, L.Y., Zheng, L., Lan, T., Wang, L.F. & Liang, G.D. (2007). Duration of antibody responses after severe acute respiratory syndrome. Emerging Infectious Diseases, 13, 1562–1564.
[70] Carsetti, R., Zaffina, S., Mortari, E., Terreri, S., Corrente, F., Capponi, C., Palomba, P., Mirabella, M., Cascioli, S., Palange, P. & Cuccaro, I. (2020). Spectrum of Innate and Adaptive Immune Response to SARS CoV 2 Infection Across Asymptomatic, Mild and Severe Cases; a Longitudinal Cohort Study. medRxiv.
[71] Edridge, A., Kaczorowska, J., Hoste, A., Bakker, M., Klein, M., Jebbink, M. & Sastre, P. (2020). Coronavirus Protective Immunity Is Short-Lasting. MedRxiv.
[72] Kissler, S.M., Tedijanto, C., Goldstein, E., Grad, Y.H. & Lipsitch, M. (2020). Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science, 368, 860–868.
[73] Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J. & Qi, F. (2020). Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv.
[74] Huang, T., Garcia-Carreras, B., Hitchings, D., Yang, B., Katzelnick, C., Rattigan, M. & Lessler, J. (2020). A Systematic Review of Antibody Mediated Immunity to Coronaviruses: Antibody Kinetics, Correlates of Protection, and Association of Antibody Responses with Severity of Disease. medRxiv.
[75] Aqel, F. (2020). Antibodies, immunity low after COVID-19 recovery [Online]. Available at: https://www.dw.com/en/coronavirus-antibodies-immunity/a-54159332. Accessed 5/7/2022.
[76] Azamor, J., T. & Bom, A. (2020). Elgaço. Protective immunity after COVID-19 has been questioned: What can we do without SARS-CoV-2-IgG detection?
[77] Roos, R. (2020). Chinese study: Antibodies in COVID-19 patients fadequickly [Online] Available at: Chinese study: Antibodies in COVID-19 patients fade quickly. Accessed 5/7/2022.
[78] Altmann, D.M. (2020). Adaptive immunity to SARS-CoV-2. Oxford Open Immunology, 1, iqaa003.
[79] Chowdhury, M.A., Hossain, N., Kashem, M.A., Shahid, M.A. & Alam, A. (2020). Immune response in COVID-19: A review. Journal of Infection and Public Health, 13, 1619–1629.
[80] Ahrends, T., Busselaar, J., Severson, T., Bąbała, N., de Vries, E., Bovens, A. & Borst, J. (2019). CD4+ T cell help creates memory CD8+ T cells with innate and help-independent recall capacities. Nature Communications, 10, 1–13.
[81] Bettelli, E., Oukka, M. & Kuchroo, V.K. (2007). TH-17 cells in the circle of immunity and autoimmunity. Nature Immunology, 8, 345–350.
[82] Grifoni, A., Weiskopf, D., Ramirez, S.I., Mateus, J., Dan, J.M., Moderbacher, C.R., Rawlings, S.A., Sutherland, A., Premkumar, L., Jadi, R.S., Marrama, D., de Silva, A.M., Frazier, A., Carlin, A.F., Greenbaum, J.A., Peters, B., Krammer, F., Smith, D.M., Crotty, S. & Sette, A. (2020). Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell, 181, 1489–1501.e15.
[83] Weiskopf, D., Schmitz, K., Raadsen, M., Grifoni, A., Okba, N., Endeman, H. & Haagmans, B. (2020). Phenotype of SARS-CoV-2-specific T-Cells in COVID-19 Patients with Acute Respiratory Distress Syndrome. medRxiv.
[84] Braun, J., Loyal, L., Frentsch, M., Wendisch, D., Georg, P., Kurth, F. & Baysal, E. (2020). Presence of SARS-CoV-2 Reactive T Cells in COVID-19 Patients and Healthy Donors. medRxiv.

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