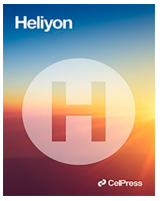
Heliyon 10 (2024) e34577

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Immune responses in COVID-19 patients: Insights into cytokine storms and adaptive immunity kinetics

Junguo Zhang

Pulmonology Department, Fengdu General Hospital, Chongqing, 408200, China

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Adaptive immunity
Cytokine storm
Immune memory

ABSTRACT

SARS-CoV-2 infection can trigger cytokine storm in some patients, which characterized by an excessive production of cytokines and chemical mediators. This hyperactive immune response may cause significant tissue damage and multiple organ failure (MOF). The severity of COVID-19 correlates with the intensity of cytokine storm, involving elements such as IFN, NF-κB, IL-6, HMGB1, etc. It is imperative to rapidly engage adaptive immunity to effectively control the disease progression. $CD4^+$ T cells facilitate an immune response by improving B cells in the production of neutralizing antibodies and activating $CD8^+$ T cells, which are instrumental in eradicating virus-infected cells. Meanwhile, antibodies from B cells can neutralize virus, obstructing further infection of host cells. In individuals who have recovered from the disease, virus-specific antibodies and memory T cells were observed, which could confer a level of protection, reducing the likelihood of re-infection or attenuating severity. This paper discussed the roles of macrophages, IFN, IL-6 and HMGB1 in cytokine release syndrome (CRS), the intricacies of adaptive immunity, and the persistence of immune memory, all of which are critical for the prevention and therapeutic strategies against COVID-19.

1. Introduction

With the decline of dead caused by the 2019 Coronavirus Disease (COVID-19), reduction in COVID-19-associated hospitalizations and severe cases [1], as well as enhancement in community immunity against the novel coronavirus (SARS-CoV-2). The World Health Organization (WHO) proclaimed the COVID-19 outbreak no longer constituted a public health emergency of international concern on May 4, 2023, at the fifteenth session of the Emergency Committee convened under the International Health Regulations (2005) [2]. This announcement signified the epidemic shift toward a stage of sustained management. Despite this progress, the continual evolution and potential for immune evasion by SARS-CoV-2 introduced elements of unpredictability [2]. By November 2023, WHO reported the total number of confirmed COVID-19 cases had reached 772 million globally, with a death of 69.88 million while the number of fatalities may surpass 20 million actually [1,3], reflecting a profound impact on both public health and the global economy.

SARS-CoV-2, the third beta coronavirus following MERS-CoV and SARS-CoV [4], is a single-stranded, positive-sense RNA virus comprising an RNA genome, envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein, and spike (S) protein [4,5]. The S protein binds to angiotensin-converting enzyme 2 (ACE2) receptors on host cells and is cleaved by transmembrane serine protease 2 (TMPRSS2) [6], facilitating viral and cellular membrane fusion and subsequent viral RNA release into the cytoplasm [7–9]. Besides ACE2-mediated entry, the virus can internalize via phagocytosis, acidification within the engulfing vesicles activates Cathepsin L

E-mail address: 13896669865@qq.com.

https://doi.org/10.1016/j.heliyon.2024.e34577
Received 29 January 2024; Received in revised form 11 July 2024; Accepted 11 July 2024
Available online 14 July 2024

(CTSL), triggering fusion with the endosomal membrane and release of viral RNA [10–12]. The virus then replicate, assemble, and are released intracellularly. SARS-CoV-2 can also utilize other receptors like KREMEN1 [13], ASGR1 [13], and CD147 [14] to infect various cells. The innate immune response, comprising cytokine release and the activation of adaptive immunity—antibodies from B lymphocytes and T lymphocyte-mediated immunity ($CD4^+$ Th cells and $CD8^+$ Tc cells)—constitute the body's initial defense [15]. Studies indicated that the immune dysregulation after SARS-CoV-2 infection may persist beyond two years [16–18]. This review explored the immune dynamics in body post-SARS-CoV-2 infection.

2. Cytokine storm

In patients critically ill with COVID-19, we observed a marked elevation in cytokine levels, leading to CRS. This syndrome encompasses the increase of various cytokines, such as IL-6, IL-8, IL-12, TNFα, IL-17, MCP-1, IP-10, and IL-10. The surge of cytokine triggers an immune imbalance and promotes inflammatory responses, infiltration by neutrophils and macrophages, and consequent pulmonary damage [15].

2.1. The role of alveolar macrophages in CRS

Alveolar macrophages (AMs), occupying up to 95 % of the alveolar immune cell population, are a key component of pulmonary defense, primarily distributed across the surface and deeper strata of pulmonary surfactant (PS) [12]. These cells are the alveoli's initial safeguard against microbial threats [19]. Typically assuming an M2 phenotype under physiological conditions, AMs maintain a higher intracellular pH [12], suppressing the activity of cathepsin L (CTSL) and thus thwarting the release of viral RNA into the cytoplasm [10]. M2 macrophages secrete an array of growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF)-α, and insulin-like growth factor 1 (IGF-1), which are indispensable for angiogenesis and cellular proliferation, and thereby instrumental in tissue restoration post-injury. Conversely, SARS-CoV-2 prompts a shift in AM phenotype from M2 to M1. These M1 AMs, with stronger acidic intracellular milieu, can further favor viral replication [12]. Enhanced phagocytosis by M1 AMs also aids in viral propagation [10]. Concurrently, M1 AMs release pro-inflammatory cytokines such as TNF-α and IL-6, impeding the release of surfactant compounds by alveolar type II epithelial cells and disrupting PS structure. Inflammatory events lead to increased secretion of cytokines and chemokines, including IL-6, IFN-γ, MCP1, and IP-10,[20] which draw monocytes, T lymphocytes, and other immune cells to the infection site [21]. Critically ill patients exhibited higher IL-6 levels, than milder cases persistently [22–24], and showed a pronounced rise in the proportion of $CD14^+$, $CD16^+$, and inflammatory cells in the peripheral blood [25], aggravating the cytokine storm depicted in Fig. 1.

2.2. Type I IFN

Dendritic cells (DCs) initiate the immune system's response to pathogens, with the engagement of conventional DCs (cDCs) and plasmacytoid DCs (pDCs) in the secretion of interferons (IFNs), particularly Type I IFNs α and β[15]. During SARS-CoV-2 infection, pDCs

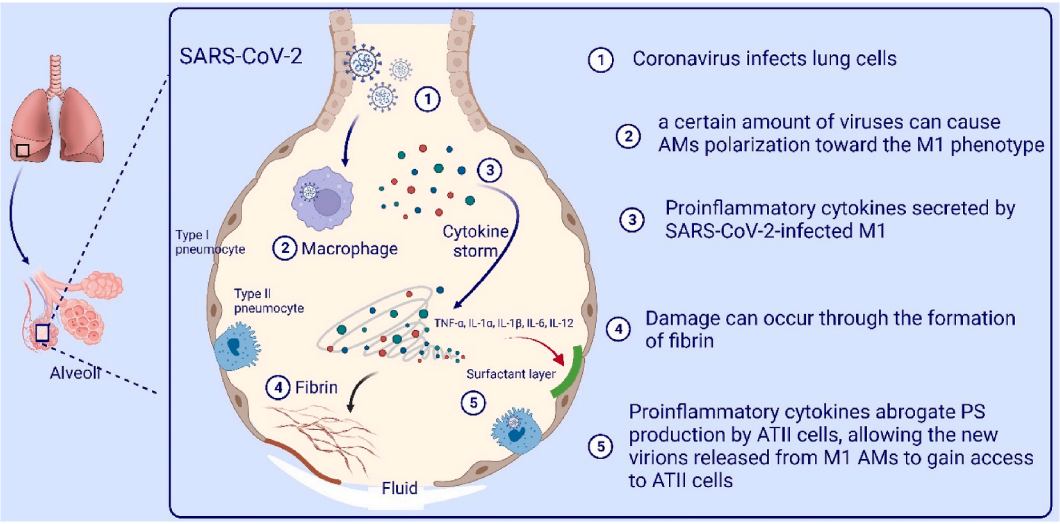


Fig. 1. illustrated the pathophysiological cascade following SARS-CoV-2 invasion of lung. Virus triggers the differentiation of AM into the M1 phenotype. These M1 AM release pro-inflammatory cytokines to precipitate local inflammation. This inflammation escalates the production of pro-inflammatory cytokines and chemokines, which contribute to CRS. Concurrently, the inflammatory mediators suppress the formation of protective surfactant (PS), while the viral progeny propagated by M1 cells continue to infect type II alveolar epithelial cells (ATII), further exacerbating the condition.

express Toll-like receptors 7 (TLR-7) and 9 (TLR-9), which activate a cascade via myeloid differentiation primary response 88 (MyD88) and IRF-7, leading to substantial production of IFN-α/β—a critical factor in defense [15]. Meanwhile, cDCs elicit an inflammatory response by releasing cytokines such as IL-12 and TNF-α. Appropriate production of Type I IFN can significantly impede viral replication and engage adaptive immune system. Nonetheless, severe COVID-19 cases exhibit impaired IFN responses, thereby amplifying viral proliferation and delaying acquired immunity. This delayed response precipitates expansive immune activation, resulting in chronic cytokine emission, intensifying inflammation, and potentially culminating in a perilous CRS [26], as elucidated in Fig. 2. Those cytokines were further produced to activate adaptive immune system through monocytes and lymphocytes [27]. Therefore, timely production of Type I IFN by host cells can effectively inhibit virus and activate adaptive immunity. However, in severe COVID-19 cases, the response to IFN-I will be delayed and reduced, leading to increased replication of the SARS-CoV-2 virus [28–31] and delayed acquired immunity, and the innate immune system controls virus by expanding immune responses. This leads to continuous release of cytokines such as IL-6, TNFα, promoting inflammatory responses, immune amplification, hyperimmunity, and potentially progressing to CRS [15,30].

2.3. HMGB1

High mobility group (HMG) is a non-histone chromosome-binding protein in eukaryotic cells [1]. Based on HMG molecular weight, structural similarity and DNA-binding properties, HMG proteins have been classified into three gene families: HMGA, HMGB and HMGN. HMGB1 is the most abundant non-histone nuclear protein in the HMGB gene family [32]. HMGB1 has a dual function as both a non-histone nuclear protein and an extracellular inflammatory cytokine. Intracellular HMGB1 binds extensively to DNA and is involved in transcriptional regulation, DNA replication and repair, telomere maintenance and nucleosome assembly. Extracellular HMGB1 is passively released or actively secreted by necrotic tissue or stressed cells. As a chemokine or cytokine, it binds to pattern recognition receptors (PRR) and exerts damage-associated molecular patterns (DAMP) effects [33]. Pathogen-associated molecular patterns (PAMPs) and DAMPs are critical in triggering the hyperactive immune response of severe COVID-19 cases [34], as they are notably present in blood and lung [35]. PAMPs initiate the activation of PRRs, propelling downstream signaling cascades that result in the release of cytokines such as interleukins (ILs), tumor necrosis factor (TNF), and IFNs [25]. Meanwhile, DAMPs, which are ubiquitously expressed and can be liberated passively from necrotic cells, engage PRRs as well, potentially leading to immune dysregulation and pronounced inflammatory responses which threaten patients' survival [36,37].

HMGB1 has been emerged as a pivotal DAMP in this context. There are two known nuclear localization signaling (NLS) sites on the HMGB1 protein, NLS1 and NLS2.Stimulated by inflammatory responses triggered by DAMPs or PAMPs, they are modified by

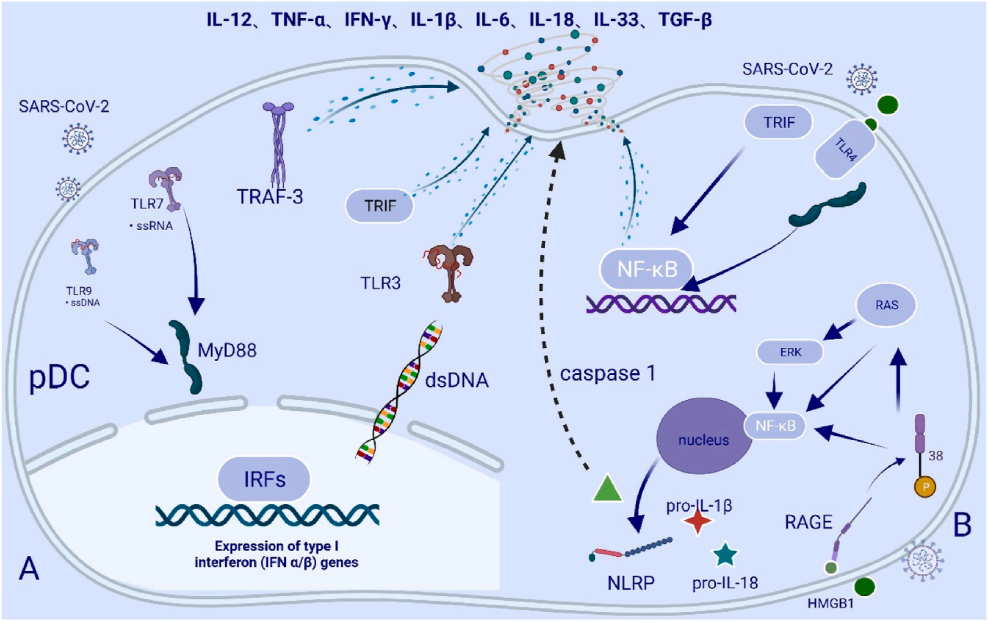


Fig. 2. Upon invasion by SARS-CoV-2, pDCs express TLR-7 and TLR-9, initiating signaling through MyD88 and IRF-7 that induce type I IFN responses, resulting in the substantial secretion of IFN-α/β. Subsequently, dsRNA activates TLR-3 through the involvement of TRIF and TRAF-3, culminating in the release of NF-κB and numerous pro-inflammatory cytokines. The interaction between HMGB1 and TLR4 triggers the TLR signaling pathway through the intermediation of MyD88 and TRIF. Subsequently, this leads to the activation of NF-κB. Concurrently, the binding of HMGB1 to the RAGE initiates the Ras-mediated activation of ERK and p38, culminating in NF-κB pathway activation. This sequence of events promotes the translocation of NF-κB to the nucleus, fostering the transcription of various proinflammatory genes and synthesis of pro-IL-1β, pro-IL-18, IL-6 and TNF-α. Caspase 1 processes pro-IL-1β and pro-IL-18 into their mature forms, IL-1β and IL-18, thereby contributing to CRS associated with SARS-CoV-2 infection.

phosphorylation and acetylation, respectively, to promote the nuclear localization of HMGB1, thereby transporting HMGB1 from the nucleus to the cytoplasm, and the transfer of HMGB1 in the cytoplasm can be achieved by the induction of type I and type II IFNs; after that, HMGB1 secretes lysosome formation or programmed cell death mechanisms to be released into the extracellular fluid [37]. Toll-like receptor 4(TLR4) and receptor for advanced glycation end products (RAGE) serve as HMGB1's functional PRRs [38]. Interaction with TLR4 activates MyD88 and TRIF-dependent pathways, culminating in NF-κB and interferon regulatory factor 3 (IRF3) activation, thus amplifying inflammatory cytokine and IFN production [39]. Upon interaction with RAGE, HMGB1 triggers the activation of Ras, leading to the stimulation of the NF-κB pathway. This signaling cascade involves extracellular regulated protein kinases (ERK) and p38, which facilitate the translocation of NF-κB from the cytoplasm to the nucleus [34]. Subsequently, this process activates the transcription of various pro-inflammatory genes, induces the formation of inflammatory vesicles like NOD-like receptor thermal protein domain associated protein 3(NLRP3), and promotes the production of pro-IL-1β, pro-IL-18, IL-6, and TNF-α. Enhanced NLRP3 activity has been corroborated in severely ill patients [40], further intensifying caspase-1 activity [41], which not only processes pro-IL-1β and pro-IL-18 into their active forms [34], but also activates IL-1α through Gasdermin-D (GSDMD), thus contributing to the CRS driven by SARS-CoV-2 [42], as depicted in Fig. 2. IL-18, belonging to the IL-1 family, augments natural killer (NK) cell cytotoxicity and is a potent IFN-γ inducer [43]. Persistently elevated IL-18 is also implicated as a principal contributor to CRS [43,44]. Collectively, in COVID-19, the HMGB1-RNA (SARS-CoV-2) complex perpetuates an escalated output of pro-inflammatory cytokines, fostering a detrimental feedback loop.

2.4. Key pro-inflammatory mechanism of IL-6 in CRS

IL-6 plays a critical role in SARS-CoV-2 infection and CRS, exerting both pro-inflammatory and anti-inflammatory actions. This cytokine engages IL-6R and activates the STAT3 pathway by Glycoprotein130 (gp-130) [15]. Three distinct signaling mechanisms mediate IL-6 signal transduction: (1) The classical pathway involves IL-6 binding with membrane-bound IL-6R to form a complex that associates with gp-130, triggering signal transduction that influences the adaptive immune system, including B and T lymphocytes, potentially leading to CRS. (2) *Trans*-signalling: aberrant regulation of IL-6 *trans*-signalling plays a key role in the development of SCR in COVID-19 patients [45]. High levels of IL-6 release induced by SARS-CoV-2 infection result in the formation of a complex of IL-6 with the soluble IL-6 receptor (sIL-6R) and signaling through the membrane-bound gp130 signal transduction sub unit for signaling [45,46]. This cross-signaling mechanism also leads to depletion of immune cells, which in turn leads to respiratory failure and multi-organ failure [47]. (3) Interaction with membrane-bound IL-6R (mIL-6R) on immune cells forms a complex with gp-130 on Helper T cell 17 (Th17), which modulates T cell signaling and facilitates the progression of acute respiratory distress syndrome (ARDS) [15]. Additionally, IL-6, in conjunction with IL-23 and TNF-α, promote the differentiation of naive Th cells into Th17 cells [48], which secrete the potent pro-inflammatory cytokine IL-17, observed in abundance in COVID-19. IL-17 activates an array of cytokines and chemokines like IL-1, IL-6, IL-8, IL-21, MCP-1, and TNF-α, exacerbating CRS [49]. Moreover, IL-6 and IL-17 act synergistically to boost the expression of pro-survival genes such as Bcl-2 and Bcl-xL, impeding apoptosis in infected cells and facilitating viral persistence. This infiltration of IL-6 and Th17 is pivotal in ARDS initiation and progression [15]. In COVID-19, elevated IL-6 may suppress the activity of NK cells and $CD8^+$ T cells, enhancing the inflammatory cascade and disease severity [50,51], potentially by dampening NK cell cytotoxicity through diminished release of perforin and granzyme [51,52]. Macrophages, key to innate immunity, primarily recognize RNA viruses through PRRs such as TLR, RIG-I, and MDA5, which activate NF-κB and IRF3/7 pathways and promote the production of pro-inflammatory cytokines, CXCL10, ITAM, and TRAM [30,53–55], thereby stimulating macrophages to release copious inflammatory mediators. Recent findings suggested that IL-6R signaling may spur bone marrow proliferation and foster tissue migration during acute infections, leading to monocyte accumulation in the lungs [16]. In severe COVID-19 cases, IL-6R activation can effect transcription factors' epigenetic modulation, enhance bone marrow proliferation, and alter the genetic phenotype of granulocyte-macrophage progenitor cells (GMP) [16], making IL-6R blockade a potential target for modifying GMP's genetic phenotype.

In summary, the immune mechanisms of CRS in patients with COVID-19 are very complex, and studies of drugs targeting cytokines or cytokine receptors are unsatisfactory.Chloroquine inhibits HMGB1 and Toll-like receptor 9, but its therapeutic efficacy in COVID-19 is not satisfactory due to the lack of a precise target [56]. Only the IL-6 receptor-targeting antibodies tolizumab and sarilizumab have more positive efficacy in COVID-19 critically ill patients [57,58]. Future drug studies need to explore precise target therapy, such as IL-6 *trans*-signalling, RAGE and TLR4 targets.

3. Adaptive immunity induced by SARS-CoV-2

B lymphocytes, $CD4^+$ T cells, and $CD8^+$ T cells are critically involved in the control and eradication of viral infections and are integral to vaccine efficacy. Consequently, researches on SARS-CoV-2's adaptive immunity are paramount. Typically, the innate immune system rapidly detects viral infection within hours, initiating a Type I IFN response and provoking the release of immune mediators [59]. It impedes viral replication and the congregation of both innate immune cells and molecules, curbing the virus's spread. The paramount function of innate immunity, however, lies in its capacity to activate the adaptive immune response. Adaptive immune cells undergo a phase of brisk proliferation and differentiation, taking approximately 6–10 days to become effectual. SARS-CoV-2 is able to postpone the activation of cellular IFN-I and IFN-III responses associated with innate immunity [60], resulting in an early lack of viral replication control. This latency can cause asymptomatic infections [61]. Investigations involving patients in both acute and recovery phases of COVID-19 have revealed a significant association between SARS-CoV-2-specific T cell responses and milder symptoms [23,62], underscoring the potential criticality of T cells in rapidly curtailing SARS-CoV-2 infection.

3.1. Adaptive immunity resulting from SARS-CoV-2 infection

The human immune response effectively combats SARS-CoV-2 primarily through the action of SARS-CoV-2-specific antibodies, $CD4^+$ T cells, and $CD8^+$ T cells [63,64], which are pivotal in managing viral infections, as depicted in Fig. 3. Notably, there is a pronounced correlation between specific $CD4^+$ T cell responses and the severity of COVID-19 cases [65].

3.1.1. $CD4^+$ T cells

Studies had indicated that $CD4^+$ T cells elicit a more potent response to SARS-CoV-2 than $CD8^+$ T cells [62,63], with their detectable reactivity in the majority of COVID-19 patients [62,63,65]. Individuals who had recovered from COVID-19 exhibit $CD4^+$ T cell responses to an extensive array of SARS-CoV-2 proteins, notably the M, S, and N antigens, although a small subset of proteins remains unrecognized by these cells [63]. The M protein—an inherently modest transmembrane protein involved in multiple channels—serves as one of the antigens for $CD4^+$ T cells, although it demonstrates relatively low binding affinity to Class II MHC-restricted T cells [66]. In contrast, the S protein is recognized as a significant antigen of SARS-CoV-2 [63,65,67,68], with roughly half of specific $CD4^+$ T cell responses associated with it, and is vital for Major Histocompatibility Complex (MHC) class II molecule recognition. $CD4^+$ T cells predominantly differentiate into Th1 and follicular helper T cells (TFH), where Th1 cells contribute to antiviral defense by secreting IFN-γ and associated cytokines, while TFH cells are integral to neutralizing antibodies, memory B cell formation, and sustained humoral immunity [69].

During the acute phase of SARS-CoV-2 infection, specific circulating follicular helper T cells (cTFH) are generated, including memory cTFH cells [62,65,70]. The presence of SARS-CoV-2-cTFH has been associated with disease severity [65]. Predominantly, SARS-CoV-2-specific $CD4^+$ T cells produce IFN-γ and can differentiate into cytotoxic T cells (CD4-CTL), directly contributing to viral clearance [65,67,71]. These cells also recruit additional effector cells to areas with viral antigens by emitting chemokines such as CCL3/4/5 (MIP-1s) and XCL1 [70]. Additionally, there is a potential for specific $CD4^+$ T cells to become Th17 cells, releasing IL-22 which is vital for tissue restoration, particularly in lung. Study indicated that mucosal $CD4^+$ T cells stably express IL-22, implying that these cells may facilitate lung tissue repair [63,65,72]. Memory $CD4^+$ T cells targeting SARS-CoV-2 also appear to retain the capability to produce IL-22[65]. Moreover, $CD4^+$ T cells may support the $CD8^+$ T cell immune response, with IL-21 potentially plays a key role [73], although the precise mechanism remains to be fully elucidated.

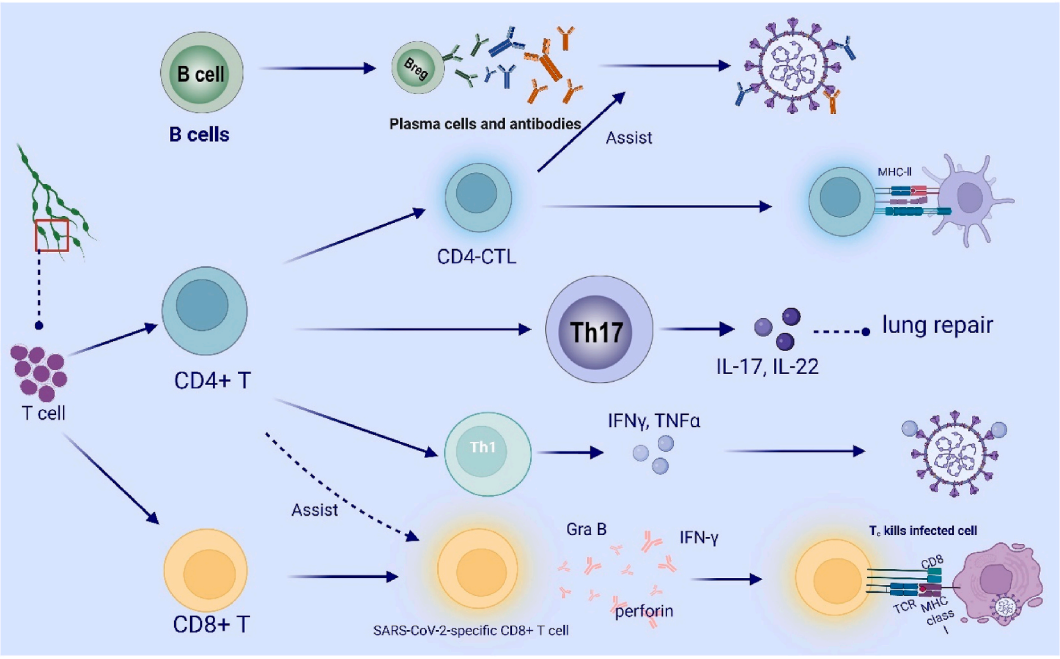


Fig. 3. illustrated that the S and N proteins of SARS-CoV-2 constitute the primary antigens for generation of specific antibodies. Upon activation of the adaptive immune response, select B cells transform into plasma cells that produce quantities of antibodies, including IgM, IgA, IgG, and neutralizing antibodies, which function to directly neutralize virus. Concurrently, another subset of B lymphocytes mature into memory cells for long-term immunity. SARS-CoV-2-specific $CD4^+$ T cells predominantly secrete IFN-γ and often differentiate into T helper 1 (Th1) and T follicular helper (TFH) cells. Th1 cells promote antiviral responses through the production of IFN-γ and associated cytokines, whereas TFH cells are integral to the generation of neutralizing antibodies, the sustenance of memory B cells, and the establishment of enduring humoral immunity. Additionally, specific $CD4^+$ T cells may become Th17 cells, releasing interleukin-22 (IL-22) to aid in the repair of lung tissue. SARS-CoV-2-specific $CD8^+$ T cells show elevated levels of activation markers and cytotoxic molecules, playing a pivotal role in the eradication of the virus and infected host cells.

3.1.2. $CD8^+$ T cells

SARS-CoV-2-specific $CD8^+$ T cells demonstrate specificity to a plethora of viral antigens, including the S, N, and M proteins, along with ORF3a and NSP6 [63,68,74]. Furthermore, the predominant fraction of SARS-CoV-2-specific $CD8^+$ T cell response is identifiable through HLA-I class molecules [63]. During acute COVID-19, these cells manifest pronounced cytotoxic effects, marked by the expression of molecules such as IFN-γ, granzyme B, and perforin [62,65,75]. Notably, there exists a considerable overlap in T-cell receptor (TCR) repertoires between cytotoxic and memory subsets of $CD8^+$ T cells [76], leading to a resemblance in the expression profiles of memory SARS-CoV-2-specific $CD8^+$ T cells [62,63,65,68]. Research indicated [77] that post-infection, memory $CD8^+$ T cells bifurcate into two distinct subsets: early fase memory cells, which arise during the initial stages of infection and display heightened activation and cytotoxic potential with broad antigen specificity; late fase memory cells, which emerge in the subsequent phases, characterized by reduced activation, diminished cytotoxic molecule expression, and a more restricted antigen specificity.

Exposure to SARS-CoV-2 antigens markedly influences the phenotype and specificity of memory $CD8^+$ T cells, which exhibit higher activation markers and cytotoxic molecule expression upon repeated encounters with virus, leading to an enriched T cell memory repertoire. Sarah Adamo and his colleagues [78], using flow cytometry and single-cell RNA sequencing, observed the evolution of specific memory $CD8^+$ T cells post-infection. These cells, displaying distinct phenotypic and functional traits, are vital in providing resistance to subsequent SARS-CoV-2 infections [75]. Moreover, research conducted by Anthony Kusnadi and Ciro Ramírez-Suástegui highlighted the differences in $CD8^+$ T cell responses among COVID-19 patients [79]; those with mild symptoms tended to have a predominance of "exhausted" SARS-CoV-2 reactive $CD8^+$ T cells, whereas severe cases exhibited "non-exhausted" cells, characterized by transcripts indicative of co-stimulation, NF-κB signaling, and anti-apoptotic pathways—suggesting the generation of strong memory response. The correlation of $CD8^+$ T cell dynamics with COVID-19 outcomes is further supported by Katie E Lineburg and associates [80], who demonstrated that SPRWYFYYLN105-113 (SPR) specific $CD8^+$ T cells could be identified both in individuals recovered from COVID-19 and those with no prior SARS-CoV-2 exposure, implying a potential cross-reactive immunity from seasonal coronaviruses. The persistence of the SPR epitope indicated its potential role in long-term protection against the virus [80].

3.1.3. B lymphocytes

In the majority of individuals infected with SARS-CoV-2, seroconversion typically occurs within 5–15 days post-infection, with approximately 90 % will experience seroconversion by day 10[65,81,82]. The S and N proteins serve as principal antigens for detecting seroconversion. Specifically, the receptor-binding domain (RBD) of the S protein is the focal point for over 90 % of the neutralizing antibodies [83,84]. MHC Class I molecules assume an "up" conformation when engaging with the RBD, while MHC Class II molecules can present in both "up" and "down" configurations [85]. The neutralizing antibodies, developed by B cells with a diversity of heavy and light chain variable (V) genes [86,87], tend to be readily produced against SARS-CoV-2 as they require minimal to no affinity maturation [88]. During antigen presentation, MHC Class I and II molecules present the processed antigens to T cells, which then coalesce to eliminate the infected cells and regulate the immune response. Concurrently, some B cells commence differentiation into plasma cells that secrete copious antibodies. Importantly, IgM play a crucial role in the initial response to infection as the first antibody produced. The B cell reaction to SARS-CoV-2 is pivotal for generating an effective neutralizing antibody defense.

Following an initial IgM response, there is a shift in the profile of secreted antibodies, predominantly to IgG (mainly subtypes 1 and 3) and IgA [89]. IgG titer elevate over several months after acute infection, with the concentration of IgG1 appearing higher than those of IgG3 subsequent in SARS-CoV-2 cases [90]. The transition to IgA is strongly influenced by the severity of clinical symptoms, which means patients with more pronounced COVID-19 symptoms exhibit elevated IgA titers, conferring protection to the mucosa of the respiratory tract [91]. As COVID-19-induced inflammation intensifies, antibody production within the body increases [92]. Patients requiring intensive care for prolonged durations present the highest levels of neutralizing antibodies. In contrast, children exhibit lower antibody titers when compared to adults [89,93]. Additionally, a subset of B cells differentiate into memory B cells, which can persist for several months. These memory B cells, along with memory T cells, play a pivotal role in long-term immunity against SARS-CoV-2 [94].

3.2. Immune response induced by vaccines

COVID-19 mRNA vaccines are known to stimulate the maturation of CD4+T and CD8+T lymphocytes [95], and to generate B lymphocytes alongside high levels of IgG and IgM antibodies [96]. That levels of RBD memory B lymphocytes elicited by these vaccines are on par with those resulting from natural infection [96]. Research had demonstrated that memory T lymphocytes and B lymphocytes maintain relative stability for 3–6 months post-vaccination [97]. Valerie Oberhardt and colleagues [98], using a mouse model, investigated the immunological impacts of the SARS-CoV-2 mRNA vaccine (bnt162b2), revealed a rapid induction of durable, S protein-specific CD8+T cell response within a week of vaccination, independent of the strength of CD4+T cells and neutralizing antibodies at that time. These CD8+T cells, capable of identifying and neutralizing virus-infected cells, maintain their efficacy following a booster dose. Additionally, neutralizing antibodies serve as a critical indicator of protective immunity, with the primary goal of a vaccine being the induction of potent, specific neutralizing antibodies against the SARS-CoV-2 S protein. Studies had indicated that COVID-19 mRNA vaccines can initiate germinal center reactions and TFH cell responses specific to the SARS-CoV-2 S protein, critical to neutralizing antibody production [99,100]. Moreover, such vaccines are capable of inducing S antigen-specific IgA and IgG antibodies that sustain high titers six months following the second vaccination dose [101,102]. In examining the immune responses prompted by COVID-19 vaccines, it is essential for researchers to extend their focus beyond antibody responses to include investigations into memory cells, cellular immunity, and innate immune memory within T lymphocytes [103,104].

A longitudinal study of vaccine-induced immune responses in cancer patients revealed varying levels of sustained antibody

responses based on the treatment modalities received [105]. And another observational study found that patients with hematologic malignancies may have a lower immune response to the SARS-CoV-2 vaccine and may experience vaccine failure and infection breakthrough, especially in patients treated with rituximab [106]. Patients with end-stage renal disease (ESRD), including those undergoing hemodialysis, peritoneal dialysis, and renal transplantation, have compromised cellular and humoral immune responses, which may result in reduced immunity to the vaccine after vaccination [107]. Similarly, Another longitudinal study in hemodialysis patients demonstrated robust cellular and humoral immune responses following repeated vaccinations with mRNA SARS-CoV-2 vaccine over an extended period [108]. These findings underscored the distinct immune responses elicited by SARS-CoV-2 vaccination across diverse patient groups, emphasizing the necessity of longitudinal studies in specialized populations to inform more tailored vaccination approaches. Such insights are crucial for optimizing vaccine booster schedules and patient selection criteria.

Vaccination of pregnant women with the COVID-19 mRNA vaccine, whether in early, mid- or late pregnancy, produces a strong and long-lasting antibody response, which is passed on to the fetus through the placenta, providing protection for the newborn [109]. It has been found that after vaccination of the mother, babies have higher levels of neutralizing antibodies than babies born to mothers infected with SARS-CoV-2 [110]. Therefore, maternal vaccination provides passive protection against asymptomatic infections in early infancy. However, antibody levels decline significantly in the fetus during the first 3 months of life [111,112], and early vaccination in late pregnancy (27–31 weeks) increases the proportion of placenta-transmitted antibodies compared with late vaccination in late pregnancy (32–36 weeks) [113]. Therefore, vaccination early in late pregnancy is more likely to enhance neonatal immune protection [113,114].COVID-19 vaccination is associated with a significant increase in the levels of anti-SARS-CoV-2 IgG, IGM and IgA in breast milk, which can be passed on to the infant through breastfeeding, thus providing protection to the infant [110,115]. However, different vaccine types may affect antibody levels differently [110].

The emergence of mutant strains diminishes the effectiveness of current vaccines against the virus, increasing the risk of reinfection and immune evasion, thereby impacting the control of outbreaks. Variants like omicron XBB.1.16 [116] and omicron XBB.1.5 [117] have demonstrated significant immune evasion capabilities. The decline in neutralizing effectiveness of various vaccines against emerging variants like beta, epsilon, subsequent omicron subtypes [118], and novel variants has posed challenges in outbreak prevention and control. Moreover, frequent administration of vaccine booster doses may potentially lead to immune exhaustion, particularly with the BNT162b2 and mRNA-1273 vaccines [119]. Mucosal vaccines, by stimulating robust mucosal immunity in the respiratory mucosa, not only have the capacity to combat the disease but also to hinder SARS-CoV-2 infection and transmission at the initial viral entry and replication site [120]. However, the lack of clear markers for mucosal immunity and protection, as well as the complexity of designing clinical studies to evaluate transmissibility, present additional challenges. Emerging novel vaccine design ideas have brought about exciting developments. In an animal study [121], researchers introduced a new helper lipid, replacing ionizable lipids, which significantly enhanced the innate immunity of the SARS-CoV-2 mRNA-LNP vaccine. This optimized vaccine triggered the production of potent NAbs against various SARS-CoV-2 variants, robust Th1-biased cellular immunity, as well as strong B-cell and long-lasting plasma cell responses. Magnus A.G. Hoffmann et al. developed the EABR technique, which allows membrane

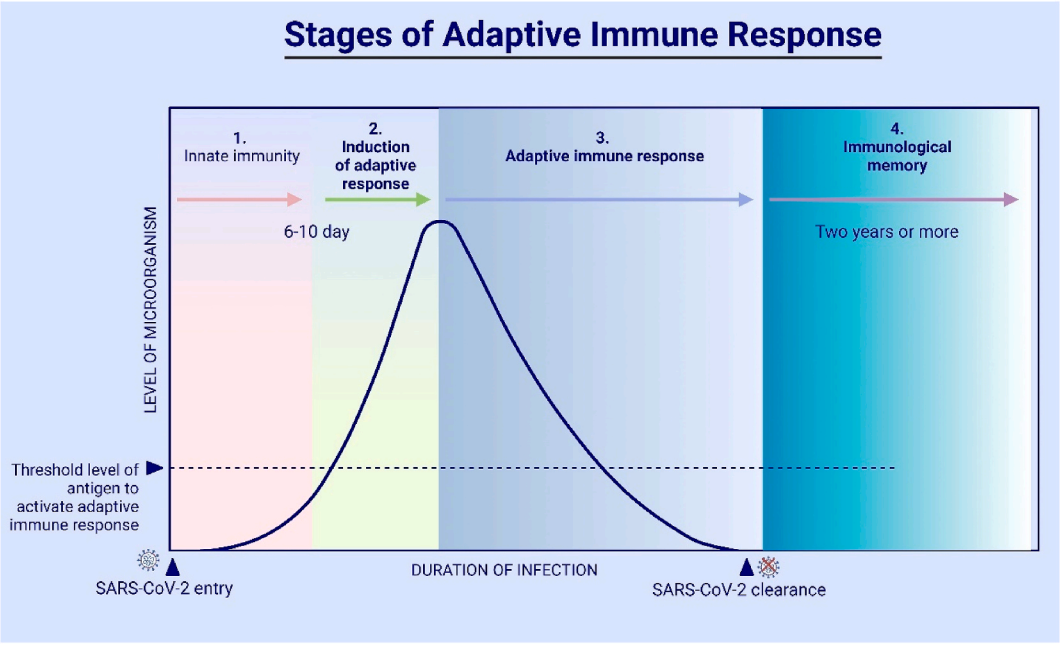


Fig. 4. illustrated the timeline of immune responses following SARS-CoV-2 infection. Typically, effector T cells and B cells proliferate in significant numbers within 6–10 days post-invasion. Subsequent to the adaptive immune system's successful eradication of the virus, an enduring immune memory is established, enduring for a variable duration. Recent studies had documented immune memory persistence for up to 2 years, marking the longest observed follow-up interval to date.

proteins to trigger the self-assembly and detachment of enveloped virus-like particles (eVLPs). This results in the presentation of S proteins on both the cell surface and the detached eVLPs, leading to a significant increase in mRNA-vaccine induced antibodies and neutralizing capacity. This effect was particularly pronounced for the omicron mutant, with levels increasing by more than 10-fold [122].

In conclusion, although the effectiveness of the new crown vaccine has been proven, there are still many limitations and large individual variability.

4. Duration of protective immunity

In recent years, researches had increasingly concentrated on the longevity of immune memory elicited by natural infection with SARS-CoV-2 or by vaccination-induced immunity. Upon invasion by SARS-CoV-2, the pathogen is eradicated through a collaborative effort of the body's innate and induced adaptive immune responses, culminating in the establishment of immune memory, which is depicted in Fig. 4. This immune memory is critical in preventing subsequent infections or in reducing disease severity, representing a key factor in managing the global pandemic.

In a 2020 study, Christian Gaebler and colleagues [123] investigated the humoral memory responses in 87 cases, examining these responses at approximately 1.3 and 6.2 months post-infection. They reported that memory B cell responses to the virus remained stable, closely mirroring the duration of antigen presence. Subsequently, a 2021 prospective cohort study by Yan Zhan et al. [124] followed 121 COVID-19 convalescent patients in Xiangyang, China. It revealed that, within a year of infection, neutralizing antibodies provided lasting protection against severe reinfection in 87 % of the participants, albeit with reduced efficacy against emerging variants. This research additionally highlighted that while the total levels of RBD antibodies remained steady over the year, anti-RBD IgG and neutralizing antibodies decreased to one-third of their initial concentration. The endurance of these antibodies correlated with factors such as the severity of the initial disease and gender. Another longitudinal cohort study in China [18], which followed up with 1096 recovered COVID-19 patients, found that 82 % of patients had N-IgG, 92.5 % had S-IgG, 94.2 % had RBD-IgG, and 81.6 % had neutralizing antibodies in 12 months after SARS-CoV-2 infection (D614G, β and δ variants). However, the old and severe cases showed a decline in neutralizing antibody levels between 6 and 12 months post infection. Additionally, virus-specific T cells were detectable in all recovered patients. This study also revealed that [18], in patients who lost neutralizing antibody response, memory T cells still retained the ability to mediate cellular immunity.

A study by Sarah Adamo et al. [78] identified that a year after acute SARS-CoV-2 infection, $CD8^+$ T cells with CD45RA, IL-7 receptor-α, and TCF1 expression persisted, albeit with consistently low CCR7 expression. Kim P and Gordon SM's retrospective analysis in 2021 demonstrated that prior infection conferred substantial protection against reinfection by the Delta variant, with immunity enduring for a minimum of 13 months [125]. Many researchs corroborated these findings [126–128]. studies from China had shown that specific T cell responses critically contribute to preventing reinfection, thereby providing prolonged and variant-transcending immune defense [18]. Notably, a longitudinal cohort study in China [129], involving 1192 unvaccinated individuals recovered from COVID-19, found that although neutralizing antibody levels waned over 6 months to 2 years with a half-life of 141.2 days, memory B cell responses to the original viral strains persisted beyond 2 years, demonstrating cross-reactivity with the Delta and Omicron BA.1 variants. Remarkably, there was no significant difference in interferon-gamma and T cell responses to SARS-CoV-2 between the one and two-year marks post-infection [129], indicating a robust, enduring cross-reactive memory T cell response. Furthermore, a meta-regression analysis highlighted [130] that hybrid immunity—resulting from both infection and vaccination—afforded enhanced protection against hospitalization or severe disease at 6 months compared to prior infection or initial vaccination alone, and also offered markedly better defense against reinfection at 6 months relative to vaccine-induced immunity. Consequently, some researchers suggested that natural immunity may confer reinfection and disease protection on par with two doses of the SARS-CoV-2 vaccine [131].

Since its emergence at the end of 2021, the Omicron variant of SARS-CoV-2 has garnered worldwide attention due to its elevated transmissibility and potential to circumvent vaccine-induced immunity, posing significant challenge for sustained immune memory and defense against severe disease and reinfection [132–136]. The presence of N501Y mutations in various SARS-CoV-2 strains enhance their affinity for ACE2 [137], while K417 and E484 mutations may help the virus escape from the neutralization by N protein antibodies [138]. Yet, immunological imprinting appears to has hindered a diverse immune response to the Omicron variant, increasing selective pressure on its RBD and driving further mutations [139]. A nationwide retrospective cohort study in Singapore indicated the superior immune-evasion capabilities of the XBB Omicron lineage [140]. Additionally, a systematic review and meta-regression analysis suggested that prior infection and hybrid immunity—derived from both past infection and vaccination—confer protection against the Omicron variant and severe outcomes for at least 15 months [141]. Nonetheless, for unvaccinated individuals and the previously vaccinated, research gaps regard the protective impact of prior Omicron infection [141] and its longevity impede a comprehensive understanding of long-term immune memory following natural exposure.

5. Conclusion and prospect

Immune damage inflicted by novel coronavirus infection substantially contributes to the wide array of observed clinical symptoms. During the initial phase of immune dysregulation, elements such as macrophages, IFN, NF-κB, IL-6, and HMGB1 are pivotal, precipitating CRS. Prompt engagement of adaptive immunity is critical for effective disease management and viral elimination, explaining the severity and increased mortality risk in immunocompromised and older patients. Combined immunity offers the most robust defense. Memory T cells, which exceed neutralizing antibodies in longevity, can preserve immune memory for upwards of two

years, a fact that bears significance for COVID-19 prevention and treatment strategies. Although the intensive studies of SARS-CoV-2 had shed light on the enigmatic pathogenetic mechanisms of COVID-19, continued research is paramount to address the remaining unknowns.

F0A8 Presently, the diagnosis of CRS depends mainly on the assessment of clinical symptoms and cytokine concentration, with a notable absence of early and precise predictive biomarkers. Additionally, comprehending the enduring health consequences of CRS on individuals is crucial.

F0A8 Which form of immunity offers the greatest efficacy in safeguarding against diverse variants of a pathogen? Furthermore, is there an existing vaccine that provides broad-spectrum protection against these variants?

F0A8 Dysregulation of adaptive immunity may occur in post-COVID-19 sequelae.

F0A8 Following recovery after COVID-19, monocytes may experience sustained epigenetic modifications that substantially alter the epigenomes and transcriptomes of hematopoietic stem cells and their progenitors. This includes variations in bone marrow proliferation and antigen presentation [16]. Nonetheless, the implications of epigenetic mechanisms in tissue repair and disease pathogenesis warrant additional investigation

Despite evidences that prior infections and resulting hybrid immunity confer enduring protection against SARS-CoV-2 variants, it remains imperative to investigate the precise longevity of this protection and its effectiveness against novel variants. Further research should be expanded to encompass additional variants and extend follow-up periods, enabling a precise assessment of the persistence of immune memory. This will also inform the evaluation of the need and optimal scheduling for vaccine booster doses.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The author(s) declare financial support was received for the research, authorship, and publication of this article. This work was supported by Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau, China) (2022QNXM024).

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Junguo Zhang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] WHO, COVID-19 epidemiological update. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports, 24 November 2023.
[2] WHO, Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic, 5 May 2023.
[3] WHO, World Health Organization: the COVID-19 pandemic is no longer considered a "global health emergency, yet the COVID-19 virus continues to be lethal and mutate (2023). https://news.un.org/zh/story/2023/05/1117647.
[4] B. Bakhshandeh, Z. Jahanafrooz, A. Abbasi, M.B. Goli, M. Sadeghi, M.S. Mottaqi, M. Zamani, Mutations in SARS-CoV-2; Consequences in structure, function, and pathogenicity of the virus, Microb. Pathog. 154 (2021) 104831, https://doi.org/10.1016/j.micpath.2021.104831.
[5] A. Dömling, L. Gao, Chemistry and biology of SARS-CoV-2, Chem 6 (2020) 1283–1295, https://doi.org/10.1016/j.chempr.2020.04.023.
[6] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020), https://doi.org/10.1016/j.cell.2020.02.052.
[7] Z. Wang, Y. Zhou, L. Bao, D. Li, J. Lv, D. Wang, S. Li, W.-M. Tong, J. Liu, C. Qin, B. Huang, Escaping alveolar macrophage endosomal retention explains massive expansion of SARS-CoV-2 delta variant, Signal Transduct. Targeted Ther. 6 (2021) 431, https://doi.org/10.1038/s41392-021-00845-4.
[8] M. Ghosh, S. Basak, S. Dutta, Underlying selection for the diversity of spike protein sequences of SARS-CoV-2, IUBMB Life 74 (2022) 213–220, https://doi.org/10.1002/iub.2577.
[9] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J.-C. Zhong, A.J. Turner, M.K. Raizada, M.B. Grant, G.Y. Oudit, Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2, Circ. Res. 126 (2020) 1456–1474, https://doi.org/10.1161/CIRCRESAHA.120.317015.

[10] J. Lv, Z. Wang, Y. Qu, H. Zhu, Q. Zhu, W. Tong, L. Bao, Q. Lv, J. Cong, D. Li, et al., Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages, Cell Discovery 7 (2021) 24, https://doi.org/10.1038/s41421-021-00258-1.
[11] Z. Wang, J. Lv, P. Yu, Y. Qu, Y. Zhou, L. Zhou, Q. Zhu, S. Li, J. Song, W. Deng, et al., SARS-CoV-2 treatment effects induced by ACE2-expressing microparticles are explained by the oxidized cholesterol-increased endosomal pH of alveolar macrophages, Cell. Mol. Immunol. 19 (2022) 210–221, https://doi.org/10.1038/s41423-021-00813-6.
[12] Z. Wang, S. Li, B. Huang, Alveolar macrophages: achilles' heel of SARS-CoV-2 infection, Signal Transduct. Targeted Ther. 7 (2022) 242, https://doi.org/10.1038/s41392-022-01106-8.
[13] Y. Gu, J. Cao, X. Zhang, H. Gao, Y. Wang, J. Wang, J. He, X. Jiang, J. Zhang, G. Shen, et al., Receptome profiling identifies KREMEN1 and ASGR1 as alternative functional receptors of SARS-CoV-2, Cell Res. 32 (2022) 24–37, https://doi.org/10.1038/s41422-021-00595-6.
[14] X. Li, Z. Zhang, Z. Wang, P. Gutiérrez-Castrellón, H. Shi, Cell deaths: involvement in the pathogenesis and intervention therapy of COVID-19, Signal Transduct. Targeted Ther. 7 (2022) 186, https://doi.org/10.1038/s41392-022-01043-6.
[15] R. Pasrija, M. Naime, The deregulated immune reaction and cytokines release storm (CRS) in COVID-19 disease, Int. Immunopharm. 90 (2021) 107225, https://doi.org/10.1016/j.intimp.2020.107225.
[16] J.-G. Cheong, A. Ravishankar, S. Sharma, C.N. Parkhurst, S.A. Grassmann, C.K. Wingert, P. Laurent, S. Ma, L. Paddock, I.C. Miranda, et al., Epigenetic memory of coronavirus infection in innate immune cells and their progenitors, Cell 186 (2023), https://doi.org/10.1016/j.cell.2023.07.019.
[17] X. Gu, S. Wang, W. Zhang, C. Li, L. Guo, Z. Wang, H. Li, H. Zhang, Y. Zhou, W. Liang, et al., Probing long COVID through a proteomic lens: a comprehensive two-year longitudinal cohort study of hospitalised survivors, EBioMedicine 98 (2023) 104851, https://doi.org/10.1016/j.ebiom.2023.104851.
[18] L. Guo, G. Wang, Y. Wang, Q. Zhang, L. Ren, X. Gu, T. Huang, J. Zhong, Y. Wang, X. Wang, et al., SARS-CoV-2-specific antibody and T-cell responses 1 year after infection in people recovered from COVID-19: a longitudinal cohort study, The Lancet. Microbe 3 (2022) e348–e356, https://doi.org/10.1016/S2666-5247(22)00036-2.
[19] Y. Qiao, E.G. Giannopoulou, C.H. Chan, S.-H. Park, S. Gong, J. Chen, X. Hu, O. Elemento, L.B. Ivashkiv, Synergistic activation of inflammatory cytokine genes by interferon-γ-induced chromatin remodeling and toll-like receptor signaling, Immunity 39 (2013) 454–469, https://doi.org/10.1016/j.immuni.2013.08.009.
[20] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet (London, England) 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[21] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (2020) 420–422, https://doi.org/10.1016/S2213-2600(20)30076-X.
[22] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet (London, England) 395 (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.
[23] M. Liao, Y. Liu, J. Yuan, Y. Wen, G. Xu, J. Zhao, L. Cheng, J. Li, X. Wang, F. Wang, et al., Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19, Nat. Med. 26 (2020) 842–844, https://doi.org/10.1038/s41591-020-0901-9.
[24] F.O. Martinez, T.W. Combes, F. Orsenigo, S. Gordon, Monocyte activation in systemic Covid-19 infection: assay and rationale, EBioMedicine 59 (2020) 102964, https://doi.org/10.1016/j.ebiom.2020.102964.
[25] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (2020) 363–374, https://doi.org/10.1038/s41577-020-0311-8.
[26] A. Oeckinghaus, S. Ghosh, The NF-kappaB family of transcription factors and its regulation, Cold Spring Harbor Perspect. Biol. 1 (2009) a000034, https://doi.org/10.1101/cshperspect.a000034.
[27] V.J. Costela-Ruiz, R. Illescas-Montes, J.M. Puerta-Puerta, C. Ruiz, L. Melguizo-Rodríguez, SARS-CoV-2 infection: the role of cytokines in COVID-19 disease, Cytokine Growth Factor Rev. 54 (2020) 62–75, https://doi.org/10.1016/j.cytogfr.2020.06.001.
[28] S.R. Paludan, T.H. Mogensen, Innate immunological pathways in COVID-19 pathogenesis, Science Immunology 7 (2022) eabm5505, https://doi.org/10.1126/sciimmunol.abm5505.
[29] P. Bastard, L.B. Rosen, Q. Zhang, E. Michailidis, H.-H. Hoffmann, Y. Zhang, K. Dorgham, Q. Philippot, J. Rosain, V. Béziat, et al., Autoantibodies against type I IFNs in patients with life-threatening COVID-19, Science (New York, N.Y.) 370 (2020), https://doi.org/10.1126/science.abd4585.
[30] I.-E. Galani, N. Rovina, V. Lampropoulou, V. Triantafyllia, M. Manioudaki, E. Pavlos, E. Koukaki, P.C. Fragkou, V. Panou, V. Rapti, et al., Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison, Nat. Immunol. 22 (2021) 32–40, https://doi.org/10.1038/s41590-020-00840-x.
[31] A. Bodansky, S.E. Vazquez, J. Chou, T. Novak, A. Al-Musa, C. Young, M. Newhams, S. Kucukak, L.D. Zambrano, A. Mitchell, et al., NFKB2 haploinsufficiency identified via screening for IFN-α2 autoantibodies in children and adolescents hospitalized with SARS-CoV-2-related complications, J. Allergy Clin. Immunol. 151 (2023), https://doi.org/10.1016/j.jaci.2022.11.020.
[32] R. Kang, R. Chen, Q. Zhang, W. Hou, S. Wu, L. Cao, J. Huang, Y. Yu, X.G. Fan, Z. Yan, et al., HMGB1 in health and disease, Mol. Aspect. Med. 40 (2014) 1–116, https://doi.org/10.1016/j.mam.2014.05.001.
[33] U. Andersson, H. Yang, H. Harris, High-mobility group box 1 protein (HMGB1) operates as an alarmin outside as well as inside cells, Semin. Immunol. 38 (2018) 40–48, https://doi.org/10.1016/j.smim.2018.02.011.
[34] S. Wulandari, Hartono, T. Wibawa, The role of HMGB1 in COVID-19-induced cytokine storm and its potential therapeutic targets: a review, Immunology 169 (2023) 117–131, https://doi.org/10.1111/imm.13623.
[35] I. Naqvi, N. Giroux, L. Olson, S.A. Morrison, T. Llanga, T.O. Akinade, Y. Zhu, Y. Zhong, S. Bose, S. Arvai, et al., DAMPs/PAMPs induce monocytic TLR activation and tolerance in COVID-19 patients; nucleic acid binding scavengers can counteract such TLR agonists, Biomaterials 283 (2022) 121393, https://doi.org/10.1016/j.biomaterials.2022.121393.
[36] W.G. Land, Role of DAMPs in respiratory virus-induced acute respiratory distress syndrome-with a preliminary reference to SARS-CoV-2 pneumonia, Gene Immun. 22 (2021) 141–160, https://doi.org/10.1038/s41435-021-00140-w.
[37] H. Yang, H. Wang, S.S. Chavan, U. Andersson, High mobility group box protein 1 (HMGB1): the prototypical endogenous danger molecule, Mol. Med. (Camb.) (21 Suppl 1) (2015), https://doi.org/10.2119/molmed.2015.00087.
[38] U. Andersson, W. Ottestad, K.J. Tracey, Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? Mol. Med. (Camb.) 26 (2020) 42, https://doi.org/10.1186/s10020-020-00172-4.
[39] T. Kawasaki, T. Kawai, Toll-like receptor signaling pathways, Front. Immunol. 5 (2014) 461, https://doi.org/10.3389/fimmu.2014.00461.
[40] D.F. van den Berg, A.A. Te Velde, Severe COVID-19: NLRP3 inflammasome dysregulated, Front. Immunol. 11 (2020) 1580, https://doi.org/10.3389/fimmu.2020.01580.
[41] A.C. Ferreira, V.C. Soares, I.G. de Azevedo-Quintanilha, S.d.S.G. Dias, N. Fintelman-Rodrigues, C.Q. Sacramento, M. Mattos, C.S. de Freitas, J.R. Temerozo, L. Teixeira, et al., SARS-CoV-2 engages inflammasome and pyroptosis in human primary monocytes, Cell Death Discovery 7 (2021) 43, https://doi.org/10.1038/s41420-021-00428-w.
[42] K. Tsuchiya, S. Hosojima, H. Hara, H. Kushiyama, M.R. Mahib, T. Kinoshita, T. Suda, Gasdermin D mediates the maturation and release of IL-1α downstream of inflammasomes, Cell Rep. 34 (2021) 108887, https://doi.org/10.1016/j.celrep.2021.108887.
[43] L.H. Tjan, K. Furukawa, T. Nagano, T. Kiriu, M. Nishimura, J. Arii, Y. Hino, S. Iwata, Y. Nishimura, Y. Mori, Early differences in cytokine production by severity of coronavirus disease 2019, J. Infect. Dis. 223 (2021) 1145–1149, https://doi.org/10.1093/infdis/jiab005.
[44] H. Satış, H.S. Özger, P. Aysert Yıldız, K. Hızel, Ö. Gulbahar, G. Erbaş, G. Aygencel, O. Guzel Tunccan, M.A. Öztürk, M. Dizbay, A. Tufan, Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19, Cytokine 137 (2021) 155302, https://doi.org/10.1016/j.cyto.2020.155302.

[45] M. Rodríguez-Hernández, M. Baena-Bustos, D. Carneros, C. Zurita-Palomo, P. Muñoz-Pinillos, J. Millán, F.J. Padillo, C. Smerdou, C. von Kobbe, S. Rose-John, M. Bustos, Targeting IL-6 trans-signalling by sgp130Fc attenuates severity in SARS-CoV-2 -infected mice and reduces endotheliopathy, EBioMedicine 103 (2024) 105132, https://doi.org/10.1016/j.ebiom.2024.105132.

[46] M. Rodríguez-Hernández, D. Carneros, M. Núñez-Núñez, R. Coca, R. Baena, G.M. López-Ruiz, M.E. Cano-Serrano, A. Martínez-Tellería, A. Fuentes-López, J. M. Praena-Fernandez, et al., Identification of IL-6 signalling components as predictors of severity and outcome in COVID-19, Front. Immunol. 13 (2022) 891456, https://doi.org/10.3389/fimmu.2022.891456.

[47] S. Rose-John, B.J. Jenkins, C. Garbers, J.M. Moll, J. Scheller, Targeting IL-6 trans-signalling: past, present and future prospects, Nat. Rev. Immunol. 23 (2023) 666–681, https://doi.org/10.1038/s41577-023-00856-y.

[48] S.N. Harbour, D.F. DiToro, S.J. Witte, C.L. Zindl, M. Gao, T.R. Schoeb, G.W. Jones, S.A. Jones, R.D. Hatton, C.T. Weaver, TH17 cells require ongoing classic IL-6 receptor signaling to retain transcriptional and functional identity, Science Immunology 5 (2020), https://doi.org/10.1126/sciimmunol.aaw2262.

[49] P.J. Hotez, D.B. Corry, M.E. Bottazzi, COVID-19 vaccine design: the Janus face of immune enhancement, Nat. Rev. Immunol. 20 (2020) 347–348, https://doi.org/10.1038/s41577-020-0323-4.

[50] B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, et al., Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19), Front. Immunol. 11 (2020) 827, https://doi.org/10.3389/fimmu.2020.00827.

[51] A. Bhardwaj, L. Sapra, C. Saini, Z. Azam, P.K. Mishra, B. Verma, G.C. Mishra, R.K. Srivastava, COVID-19: immunology, immunopathogenesis and potential therapies, Int. Rev. Immunol. 41 (2022) 171–206, https://doi.org/10.1080/08830185.2021.1883600.

[52] M. Witkowski, C. Tizian, M. Ferreira-Gomes, D. Niemeyer, T.C. Jones, F. Heinrich, S. Frischbutter, S. Angermair, T. Hohnstein, I. Mattiola, et al., Untimely TGFβ responses in COVID-19 limit antiviral functions of NK cells, Nature 600 (2021) 295–301, https://doi.org/10.1038/s41586-021-04142-6.

[53] S. Jensen, A.R. Thomsen, Sensing of RNA viruses: a review of innate immune receptors involved in recognizing RNA virus invasion, J. Virol. 86 (2012) 2900–2910, https://doi.org/10.1128/JVI.05738-11.

[54] C. Quan, C. Li, H. Ma, Y. Li, H. Zhang, Immunopathogenesis of coronavirus-induced acute respiratory distress syndrome (ARDS): potential infection-associated hemophagocytic lymphohistiocytosis, Clin. Microbiol. Rev. 34 (2020), https://doi.org/10.1128/CMR.00074-20.

[55] M. Merad, J.C. Martin, Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages, Nat. Rev. Immunol. 20 (2020) 355–362, https://doi.org/10.1038/s41577-020-0331-4.

[56] R.E. Ferner, J.K. Aronson, Chloroquine and hydroxychloroquine in covid-19, Br. Med. J. Int. Ed. 369 (2020) m1432, https://doi.org/10.1136/bmj.m1432.

[57] G. Guaraldi, M. Meschiari, A. Cozzi-Lepri, J. Milic, R. Tonelli, M. Menozzi, E. Franceschini, G. Cuomo, G. Orlando, V. Borghi, et al., Tocilizumab in patients with severe COVID-19: a retrospective cohort study, The Lancet. Rheumatology 2 (2020) e474–e484, https://doi.org/10.1016/s2665-9913(20)30173-9.

[58] A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, Y.M. Arabi, D. Annane, A. Beane, W. van Bentum-Puijk, L.R. Berry, et al., Interleukin-6 receptor antagonists in critically ill patients with covid-19, N. Engl. J. Med. 384 (2021) 1491–1502, https://doi.org/10.1056/NEJMoa2100433.

[59] A.Z. Wec, D. Wrapp, A.S. Herbert, D.P. Maurer, D. Haslwanter, M. Sakharkar, R.K. Jangra, M.E. Dieterle, A. Lilov, D. Huang, et al., Broad neutralization of SARS-related viruses by human monoclonal antibodies, Science (New York, N.Y.) 369 (2020) 731–736, https://doi.org/10.1126/science.abc7424.

[60] D. Blanco-Melo, B.E. Nilsson-Payant, W.-C. Liu, S. Uhl, D. Hoagland, R. Møller, T.X. Jordan, K. Oishi, M. Panis, D. Sachs, et al., Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181 (2020), https://doi.org/10.1016/j.cell.2020.04.026.

[61] D.P. Oran, E.J. Topol, Prevalence of asymptomatic SARS-CoV-2 infection : a narrative review, Ann. Intern. Med. 173 (2020) 362–367, https://doi.org/10.7326/M20-3012.

[62] T. Sekine, A. Perez-Potti, O. Rivera-Ballesteros, K. Strålin, J.-B. Gorin, A. Olsson, S. Llewellyn-Lacey, H. Kamal, G. Bogdanovic, S. Muschiol, et al., Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19, Cell 183 (2020), https://doi.org/10.1016/j.cell.2020.08.017.

[63] A. Grifoni, D. Weiskopf, S.I. Ramirez, J. Mateus, J.M. Dan, C.R. Moderbacher, S.A. Rawlings, A. Sutherland, L. Premkumar, R.S. Jadi, et al., Targets of T Cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals, Cell 181 (2020), https://doi.org/10.1016/j.cell.2020.05.015.

[64] F. Krammer, SARS-CoV-2 vaccines in development, Nature 586 (2020) 516–527, https://doi.org/10.1038/s41586-020-2798-3.

[65] C. Rydyznski Moderbacher, S.I. Ramirez, J.M. Dan, A. Grifoni, K.M. Hastie, D. Weiskopf, S. Belanger, R.K. Abbott, C. Kim, J. Choi, et al., Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity, Cell 183 (2020), https://doi.org/10.1016/j.cell.2020.09.038.

[66] J. Mateus, A. Grifoni, A. Tarke, J. Sidney, S.I. Ramirez, J.M. Dan, Z.C. Burger, S.A. Rawlings, D.M. Smith, E. Phillips, et al., Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans, Science (New York, N.Y.) 370 (2020) 89–94, https://doi.org/10.1126/science.abd3871.

[67] J. Braun, L. Loyal, M. Frentsch, D. Wendisch, P. Georg, F. Kurth, S. Hippenstiel, M. Dingeldey, B. Kruse, F. Fauchere, et al., SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19, Nature 587 (2020) 270–274, https://doi.org/10.1038/s41586-020-2598-9.

[68] Y. Peng, A.J. Mentzer, G. Liu, X. Yao, Z. Yin, D. Dong, W. Dejnirattisai, T. Rostron, P. Supasa, C. Liu, et al., Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19, Nat. Immunol. 21 (2020) 1336–1345, https://doi.org/10.1038/s41590-020-0782-6.

[69] S. Crotty, T follicular helper cell biology: a decade of discovery and diseases, Immunity 50 (2019) 1132–1148, https://doi.org/10.1016/j.immuni.2019.04.011.

[70] B.J. Meckiff, C. Ramírez-Suástegui, V. Fajardo, S.J. Chee, A. Kusnadi, H. Simon, S. Eschweiler, A. Grifoni, E. Pelosi, D. Weiskopf, et al., Imbalance of regulatory and cytotoxic SARS-CoV-2-reactive CD4+ T cells in COVID-19, Cell 183 (2020), https://doi.org/10.1016/j.cell.2020.10.001.

[71] C.J. Knudson, M. Férez, P. Alves-Peixoto, D.A. Erkes, C.R. Melo-Silva, L. Tang, C.M. Snyder, L.J. Sigal, Mechanisms of antiviral cytotoxic CD4 T cell differentiation, J. Virol. 95 (2021) e0056621, https://doi.org/10.1128/JVI.00566-21.

[72] D. Weiskopf, K.S. Schmitz, M.P. Raadsen, A. Grifoni, N.M.A. Okba, H. Endeman, J.P.C. van den Akker, R. Molenkamp, M.P.G. Koopmans, E.C.M. van Gorp, et al., Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome, Science Immunology 5 (2020), https://doi.org/10.1126/sciimmunol.abd2071.

[73] V.R. Buchholz, D.H. Busch, Back to the future: effector fate during T cell exhaustion, Immunity 51 (2019) 970–972, https://doi.org/10.1016/j.immuni.2019.11.007.

[74] N. Le Bert, A.T. Tan, K. Kunasegaran, C.Y.L. Tham, M. Hafezi, A. Chia, M.H.Y. Chng, M. Lin, N. Tan, M. Linster, et al., SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls, Nature 584 (2020) 457–462, https://doi.org/10.1038/s41586-020-2550-z.

[75] I. Schulien, J. Kemming, V. Oberhardt, K. Wild, L.M. Seidel, S. Killmer, Sagar, F. Daul, M. Salvat Lago, A. Decker, et al., Characterization of pre-existing and induced SARS-CoV-2-specific CD8+ T cells, Nat. Med. 27 (2021) 78–85, https://doi.org/10.1038/s41591-020-01143-2.

[76] B. Zhang, R. Upadhyay, Y. Hao, M.I. Samanovic, R.S. Herati, J.D. Blair, J. Axelrad, M.J. Mulligan, D.R. Littman, R. Satija, Multimodal single-cell datasets characterize antigen-specific CD8+ T cells across SARS-CoV-2 vaccination and infection, Nat. Immunol. 24 (2023) 1725–1734, https://doi.org/10.1038/s41590-023-01608-9.

[77] A.A. Minervina, M.V. Pogorelyy, A.M. Kirk, J.C. Crawford, E.K. Allen, C.-H. Chou, R.C. Mettelman, K.J. Allison, C.-Y. Lin, D.C. Brice, et al., SARS-CoV-2 antigen exposure history shapes phenotypes and specificity of memory CD8+ T cells, Nat. Immunol. 23 (2022) 781–790, https://doi.org/10.1038/s41590-022-01184-4.

[78] S. Adamo, J. Michler, Y. Zurbuchen, C. Cervia, P. Taeschler, M.E. Raeber, S. Baghai Sain, J. Nilsson, A.E. Moor, O. Boyman, Signature of long-lived memory CD8+ T cells in acute SARS-CoV-2 infection, Nature 602 (2022) 148–155, https://doi.org/10.1038/s41586-021-04280-x.

[79] A. Kusnadi, C. Ramírez-Suástegui, V. Fajardo, S.J. Chee, B.J. Meckiff, H. Simon, E. Pelosi, G. Seumois, F. Ay, P. Vijayanand, C.H. Ottensmeier, Severely ill COVID-19 patients display impaired exhaustion features in SARS-CoV-2-reactive CD8+ T cells, Science Immunology 6 (2021), https://doi.org/10.1126/sciimmunol.abe4782.

[80] K.E. Lineburg, E.J. Grant, S. Swaminathan, D.S.M. Chatzileontiadou, C. Szeto, H. Sloane, A. Panikkar, J. Raju, P. Crooks, S. Rehan, et al., CD8+ T cells specific for an immunodominant SARS-CoV-2 nucleocapsid epitope cross-react with selective seasonal coronaviruses, Immunity 54 (2021), https://doi.org/10.1016/j.immuni.2021.04.006.
[81] Q.-X. Long, B.-Z. Liu, H.-J. Deng, G.-C. Wu, K. Deng, Y.-K. Chen, P. Liao, J.-F. Qiu, Y. Lin, X.-F. Cai, et al., Antibody responses to SARS-CoV-2 in patients with COVID-19, Nat. Med. 26 (2020) 845–848, https://doi.org/10.1038/s41591-020-0897-1.
[82] L. Premkumar, B. Segovia-Chumbez, R. Jadi, D.R. Martinez, R. Raut, A. Markmann, C. Cornaby, L. Bartelt, S. Weiss, Y. Park, et al., The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients, Science Immunology 5 (2020), https://doi.org/10.1126/sciimmunol.abc8413.
[83] P.J.M. Brouwer, T.G. Caniels, K. van der Straten, J.L. Snitselaar, Y. Aldon, S. Bangaru, J.L. Torres, N.M.A. Okba, M. Claireaux, G. Kerster, et al., Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability, Science (New York, N.Y.) 369 (2020) 643–650, https://doi.org/10.1126/science.abc5902.
[84] L. Piccoli, Y.-J. Park, M.A. Tortorici, N. Czudnochowski, A.C. Walls, M. Beltramello, C. Silacci-Fregni, D. Pinto, L.E. Rosen, J.E. Bowen, et al., Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology, Cell 183 (2020), https://doi.org/10.1016/j.cell.2020.09.037.
[85] C.O. Barnes, C.A. Jette, M.E. Abernathy, K.-M.A. Dam, S.R. Esswein, H.B. Gristick, A.G. Malyutin, N.G. Sharaf, K.E. Huey-Tubman, Y.E. Lee, et al., SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies, Nature 588 (2020) 682–687, https://doi.org/10.1038/s41586-020-2852-1.
[86] D.F. Robbiani, C. Gaebler, F. Muecksch, J.C.C. Lorenzi, Z. Wang, A. Cho, M. Agudelo, C.O. Barnes, A. Gazumyan, S. Finkin, et al., Convergent antibody responses to SARS-CoV-2 in convalescent individuals, Nature 584 (2020) 437–442, https://doi.org/10.1038/s41586-020-2456-9.
[87] T.F. Rogers, F. Zhao, D. Huang, N. Beutler, A. Burns, W.-T. He, O. Limbo, C. Smith, G. Song, J. Woehl, et al., Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model, Science (New York, N.Y.) 369 (2020) 956–963, https://doi.org/10.1126/science.abc7520.
[88] A. Sette, S. Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell 184 (2021) 861–880, https://doi.org/10.1016/j.cell.2021.01.007.
[89] X. Castro Dopico, S. Ols, K. Loré, G.B. Karlsson Hedestam, Immunity to SARS-CoV-2 induced by infection or vaccination, J. Intern. Med. 291 (2022) 32–50, https://doi.org/10.1111/joim.13372.
[90] L. Ni, F. Ye, M.-L. Cheng, Y. Feng, Y.-Q. Deng, H. Zhao, P. Wei, J. Ge, M. Gou, X. Li, et al., Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals, Immunity 52 (2020), https://doi.org/10.1016/j.immuni.2020.04.023.
[91] C. Cervia, J. Nilsson, Y. Zurbuchen, A. Valaperti, J. Schreiner, A. Wolfensberger, M.E. Raeber, S. Adamo, S. Weigang, M. Emmenegger, et al., Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19, J. Allergy Clin. Immunol. 147 (2021), https://doi.org/10.1016/j.jaci.2020.10.040.
[92] E. Shrock, E. Fujimura, T. Kula, R.T. Timms, I.H. Lee, Y. Leng, M.L. Robinson, B.M. Sie, M.Z. Li, Y. Chen, et al., Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity, Science (New York, N.Y.) 370 (2020), https://doi.org/10.1126/science.abd4250.
[93] S.P. Weisberg, T.J. Connors, Y. Zhu, M.R. Baldwin, W.-H. Lin, S. Wontakal, P.A. Szabo, S.B. Wells, P. Dogra, J. Gray, et al., Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum, Nat. Immunol. 22 (2021) 25–31, https://doi.org/10.1038/s41590-020-00826-9.
[94] L. Renia, L.F. Ng, Acquired immunity against SARS-CoV-2 infection and vaccination, EMBO Mol. Med. 15 (2023) e16345, https://doi.org/10.15252/emmm.202216345.
[95] J.W. Park, P.N.P. Lagniton, Y. Liu, R.-H. Xu, mRNA vaccines for COVID-19: what, why and how, Int. J. Biol. Sci. 17 (2021) 1446–1460, https://doi.org/10.7150/ijbs.59233.
[96] Z. Wang, F. Schmidt, Y. Weisblum, F. Muecksch, C.O. Barnes, S. Finkin, D. Schaefer-Babajew, M. Cipolla, C. Gaebler, J.A. Lieberman, et al., mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants, Nature 592 (2021) 616–622, https://doi.org/10.1038/s41586-021-03324-6.
[97] R.R. Goel, M.M. Painter, S.A. Apostolidis, D. Mathew, W. Meng, A.M. Rosenfeld, K.A. Lundgreen, A. Reynaldi, D.S. Khoury, A. Pattekar, et al., mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern, Science (New York, N.Y.) 374 (2021) abm0829, https://doi.org/10.1126/science.abm0829.
[98] V. Oberhardt, H. Luxenburger, J. Kemming, I. Schulien, K. Ciminski, S. Giese, B. Csernalabics, J. Lang-Meli, I. Janowska, J. Staniek, et al., Rapid and stable mobilization of CD8+ T cells by SARS-CoV-2 mRNA vaccine, Nature 597 (2021) 268–273, https://doi.org/10.1038/s41586-021-03841-4.
[99] J.S. Turner, J.A. O'Halloran, E. Kalaidina, W. Kim, A.J. Schmitz, J.Q. Zhou, T. Lei, M. Thapa, R.E. Chen, J.B. Case, et al., SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses, Nature 596 (2021) 109–113, https://doi.org/10.1038/s41586-021-03738-2.
[100] K. Lederer, D. Castaño, D. Gómez Atria, T.H. Oguin, S. Wang, T.B. Manzoni, H. Muramatsu, M.J. Hogan, F. Amanat, P. Cherubin, et al., SARS-CoV-2 mRNA vaccines foster potent antigen-specific germinal center responses associated with neutralizing antibody generation, Immunity 53 (2020), https://doi.org/10.1016/j.immuni.2020.11.009.
[101] N. Doria-Rose, M.S. Suthar, M. Makowski, S. O'Connell, A.B. McDermott, B. Flach, J.E. Ledgerwood, J.R. Mascola, B.S. Graham, B.C. Lin, et al., Antibody persistence through 6 Months after the second dose of mRNA-1273 vaccine for covid-19, N. Engl. J. Med. 384 (2021) 2259–2261, https://doi.org/10.1056/NEJMc2103916.
[102] S.J. Thomas, E.D. Moreira, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Pérez Marc, F.P. Polack, C. Zerbini, et al., Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine through 6 months, N. Engl. J. Med. 385 (2021) 1761–1773, https://doi.org/10.1056/NEJMoa2110345.
[103] M. Jeyanathan, S. Afkhami, F. Smaill, M.S. Miller, B.D. Lichty, Z. Xing, Immunological considerations for COVID-19 vaccine strategies, Nat. Rev. Immunol. 20 (2020) 615–632, https://doi.org/10.1038/s41577-020-00434-6.
[104] P. Mistry, F. Barmania, J. Mellet, K. Peta, A. Strydom, I.M. Viljoen, W. James, S. Gordon, M.S. Pepper, SARS-CoV-2 variants, vaccines, and host immunity, Front. Immunol. 12 (2021) 809244, https://doi.org/10.3389/fimmu.2021.809244.
[105] J.C. Figueiredo, N.M. Merin, O. Hamid, S.Y. Choi, T. Lemos, W. Cozen, N. Nguyen, L.J. Finster, J. Foley, J. Darrah, et al., Longitudinal SARS-CoV-2 mRNA vaccine-induced humoral immune responses in patients with cancer, Cancer Res. 81 (2021) 6273–6280, https://doi.org/10.1158/0008-5472.Can-21-3554.
[106] P. Langerbeins, M. Hallek, COVID-19 in patients with hematologic malignancy, Blood 140 (2022) 236–252, https://doi.org/10.1182/blood.2021012251.
[107] M. Piotrowska, M. Zieliński, L. Tylicki, B. Biedunkiewicz, A. Kubanek, Z. Ślizień, K. Polewska, P. Tylicki, M. Muchlado, J. Sakowska, et al., Local and systemic immunity are impaired in end-stage-renal-disease patients treated with hemodialysis, peritoneal dialysis and kidney transplant recipients immunized with BNT162b2 pfizer-BioNTech SARS-CoV-2 vaccine, Front. Immunol. 13 (2022) 832924, https://doi.org/10.3389/fimmu.2022.832924.
[108] M. Gonzalez-Perez, J. Baranda, M.J. Berges-Buxeda, P. Conde, M. Pérez-Olmeda, D. Lozano-Ojalvo, C. Cámara, M. Del Rosario Llópez-Carratalá, E. Gonzalez-Parra, P. Portolés, et al., Maintenance of potent cellular and humoral immune responses in long-term hemodialysis patients after 1273-mRNA SARS-CoV-2 vaccination, Pharmaceuticals 16 (2023), https://doi.org/10.3390/ph16040574.
[109] A.G. Cassidy, L. Li, Y. Golan, C. Gay, C.Y. Lin, U. Jigmeddagva, M.A. Chidboy, M. Ilala, S. Buarpung, V.J. Gonzalez, et al., Assessment of adverse reactions, antibody patterns, and 12-month outcomes in the mother-infant dyad after COVID-19 mRNA vaccination in pregnancy, JAMA Netw. Open 6 (2023) e2323405, https://doi.org/10.1001/jamanetworkopen.2023.23405.
[110] M. Selma-Royo, C. Bäuerl, D. Mena-Tudela, L. Aguilar-Camprubí, F.J. Pérez-Cano, A. Parra-Llorca, C. Lerin, C. Martínez-Costa, M.C. Collado, Anti-SARS-CoV-2 IgA and IgG in human milk after vaccination is dependent on vaccine type and previous SARS-CoV-2 exposure: a longitudinal study, Genome Med. 14 (2022) 42, https://doi.org/10.1186/s13073-022-01043-9.
[111] M.J. Muñoz-Gómez, M. Martin-Vicente, S. Vigil-Vazquez, I. Carrasco, A.H. Lobo, V. Mas, M. Vázquez, A. Manzanares, O. Cano, C. Zamora, et al., IgG antibody levels against the SARS-CoV-2 spike protein in mother-child dyads after COVID-19 vaccination, Infection 52 (2024) 813–824, https://doi.org/10.1007/s15010-023-02111-x.
[112] A. Rottenstreich, G. Zarbiv, E. Oiknine-Djian, O. Vorontsov, R. Zigron, G. Kleinstern, S. Porat, D.G. Wolf, Kinetics of maternally derived anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in infants in relation to the timing of antenatal vaccination, Clin. Infect. Dis. : an official publication of the Infectious Diseases Society of America 76 (2023) e274–e279, https://doi.org/10.1093/cid/ciac480.

[113] A. Rottenstreich, G. Zarbiv, E. Oiknine-Djian, O. Vorontsov, R. Zigron, G. Kleinstern, D.G. Wolf, S. Porat, Timing of SARS-CoV-2 vaccination during the third trimester of pregnancy and transplacental antibody transfer: a prospective cohort study, Clin. Microbiol. Infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 28 (2022) 419–425, https://doi.org/10.1016/j.cmi.2021.10.003.
[114] N. Kugelman, C. Nahshon, P. Shaked-Mishan, N. Cohen, M.L. Sher, M. Gruber, I. Marom, A. Zolotarevsky, O. Lavie, A. Damti, et al., Maternal and neonatal SARS-CoV-2 immunoglobulin G antibody levels at delivery after receipt of the BNT162b2 messenger RNA COVID-19 vaccine during the second trimester of pregnancy, JAMA Pediatr. 176 (2022) 290–295, https://doi.org/10.1001/jamapediatrics.2021.5683.
[115] Y. Golan, M. Prahl, A.G. Cassidy, C. Gay, A.H.B. Wu, U. Jigmeddagva, C.Y. Lin, V.J. Gonzalez, E. Basilio, M.A. Chidboy, et al., COVID-19 mRNA vaccination in lactation: assessment of adverse events and vaccine related antibodies in mother-infant dyads, Front. Immunol. 12 (2021) 777103, https://doi.org/10.3389/fimmu.2021.777103.
[116] D. Yamasoba, K. Uriu, A. Plianchaisuk, Y. Kosugi, L. Pan, J. Zahradnik, J. Ito, K. Sato, Virological characteristics of the SARS-CoV-2 omicron XBB.1.16 variant, Lancet Infect. Dis. 23 (2023) 655–656, https://doi.org/10.1016/S1473-3099(23)00278-5.
[117] R. Uraki, M. Ito, M. Kiso, S. Yamayoshi, K. Iwatsuki-Horimoto, Y. Furusawa, Y. Sakai-Tagawa, M. Imai, M. Koga, S. Yamamoto, et al., Antiviral and bivalent vaccine efficacy against an omicron XBB.1.5 isolate, Lancet Infect. Dis. 23 (2023) 402–403, https://doi.org/10.1016/S1473-3099(23)00070-1.
[118] N. Firouzabadi, P. Ghasemiyeh, F. Moradishooli, S. Mohammadi-Samani, Update on the effectiveness of COVID-19 vaccines on different variants of SARS-CoV-2, Int. Immunopharm. 117 (2023) 109968, https://doi.org/10.1016/j.intimp.2023.109968.
[119] M. Echaide, L. Chocarro de Erauso, A. Bocanegra, E. Blanco, G. Kochan, D. Escors, mRNA vaccines against SARS-CoV-2: advantages and caveats, Int. J. Mol. Sci. 24 (2023), https://doi.org/10.3390/ijms24065944.
[120] J.M. Knisely, L.E. Buyon, R. Mandt, R. Farkas, S. Balasingam, K. Bok, U.J. Buchholz, M.P. D'Souza, J.L. Gordon, D.F.L. King, et al., Mucosal vaccines for SARS-CoV-2: scientific gaps and opportunities-workshop report, NPJ Vaccines 8 (2023) 53, https://doi.org/10.1038/s41541-023-00654-6.
[121] X. Han, M.-G. Alameh, K. Butowska, J.J. Knox, K. Lundgreen, M. Ghattas, N. Gong, L. Xue, Y. Xu, M. Lavertu, et al., Adjuvant lipidoid-substituted lipid nanoparticles augment the immunogenicity of SARS-CoV-2 mRNA vaccines, Nat. Nanotechnol. 18 (2023) 1105–1114, https://doi.org/10.1038/s41565-023-01404-4.
[122] M.A.G. Hoffmann, Z. Yang, K.E. Huey-Tubman, A.A. Cohen, P.N.P. Gnanapragasam, L.M. Nakatomi, K.N. Storm, W.J. Moon, P.J.C. Lin, A.P. West, P. J. Bjorkman, ESCRT recruitment to SARS-CoV-2 spike induces virus-like particles that improve mRNA vaccines, Cell 186 (2023), https://doi.org/10.1016/j.cell.2023.04.024.
[123] C. Gaebler, Z. Wang, J.C.C. Lorenzi, F. Muecksch, S. Finkin, M. Tokuyama, A. Cho, M. Jankovic, D. Schaefer-Babajew, T.Y. Oliveira, et al., Evolution of antibody immunity to SARS-CoV-2, Nature 591 (2021) 639–644, https://doi.org/10.1038/s41586-021-03207-w.
[124] Y. Zhan, Y. Zhu, S. Wang, S. Jia, Y. Gao, Y. Lu, C. Zhou, R. Liang, D. Sun, X. Wang, et al., SARS-CoV-2 immunity and functional recovery of COVID-19 patients 1-year after infection, Signal Transduct. Targeted Ther. 6 (2021) 368, https://doi.org/10.1038/s41392-021-00777-z.
[125] P. Kim, S.M. Gordon, M.M. Sheehan, M.B. Rothberg, Duration of severe acute respiratory syndrome coronavirus 2 natural immunity and protection against the delta variant: a retrospective cohort study, Clin. Infect. Dis. : an official publication of the Infectious Diseases Society of America 75 (2022) e185–e190, https://doi.org/10.1093/cid/ciab999.
[126] P. Chellamuthu, A.N. Angel, M.A. MacMullan, N. Denny, A. Mades, M. Santacruz, R. Lopez, C. Bagos, J.G. Casian, K. Trettner, et al., SARS-CoV-2 specific IgG antibodies persist over a 12-month period in oral mucosal fluid collected from previously infected individuals, Front. Immunol. 12 (2021) 777858, https://doi.org/10.3389/fimmu.2021.777858.
[127] P. Dehgani-Mobaraki, A.K. Zaidi, N. Yadav, A. Floridi, E. Floridi, Longitudinal observation of antibody responses for 14 months after SARS-CoV-2 infection, Clin. Immunol. 230 (2021) 108814, https://doi.org/10.1016/j.clim.2021.108814.
[128] M. Rosati, E. Terpos, I. Ntanasis-Stathopoulos, M. Agarwal, J. Bear, R. Burns, X. Hu, E. Korompoki, D. Donohue, D.J. Venzon, et al., Sequential analysis of binding and neutralizing antibody in COVID-19 convalescent patients at 14 Months after SARS-CoV-2 infection, Front. Immunol. 12 (2021) 793953, https://doi.org/10.3389/fimmu.2021.793953.
[129] L. Guo, Q. Zhang, X. Gu, L. Ren, T. Huang, Y. Li, H. Zhang, Y. Liu, J. Zhong, X. Wang, et al., Durability and cross-reactive immune memory to SARS-CoV-2 in individuals 2 years after recovery from COVID-19: a longitudinal cohort study, The Lancet. Microbe (2023), https://doi.org/10.1016/S2666-5247(23)00255-0.
[130] N. Bobrovitz, H. Ware, X. Ma, Z. Li, R. Hosseini, C. Cao, A. Selemon, M. Whelan, Z. Premji, H. Issa, et al., Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression, Lancet Infect. Dis. 23 (2023) 556–567, https://doi.org/10.1016/S1473-3099(22)00801-5.
[131] M.E. Flacco, C.A. Martellucci, L. Manzoli, Extra data to confirm waning protection of omicron (B.1.1.529) natural immunity, Lancet (London, England) 402 (2023) 1129, https://doi.org/10.1016/S0140-6736(23)01424-1.
[132] Y. Cao, A. Yisimayi, F. Jian, W. Song, T. Xiao, L. Wang, S. Du, J. Wang, Q. Li, X. Chen, et al., BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection, Nature 608 (2022) 593–602, https://doi.org/10.1038/s41586-022-04980-y.
[133] Q. Wang, Y. Guo, S. Iketani, M.S. Nair, Z. Li, H. Mohri, M. Wang, J. Yu, A.D. Bowen, J.Y. Chang, et al., Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5, Nature 608 (2022) 603–608, https://doi.org/10.1038/s41586-022-05053-w.
[134] R. Uraki, M. Kiso, S. Iida, M. Imai, E. Takashita, M. Kuroda, P.J. Halfmann, S. Loeber, T. Maemura, S. Yamayoshi, et al., Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA.2, Nature 607 (2022) 119–127, https://doi.org/10.1038/s41586-022-04856-1.
[135] S. Cele, L. Jackson, D.S. Khoury, K. Khan, T. Moyo-Gwete, H. Tegally, J.E. San, D. Cromer, C. Scheepers, D.G. Amoako, et al., Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization, Nature 602 (2022) 654–656, https://doi.org/10.1038/s41586-021-04387-1.
[136] E. Cameroni, J.E. Bowen, L.E. Rosen, C. Saliba, S.K. Zepeda, K. Culap, D. Pinto, L.A. VanBlargan, A. De Marco, J. di Iulio, et al., Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift, Nature 602 (2022) 664–670, https://doi.org/10.1038/s41586-021-04386-2.
[137] D.P. Martin, S. Weaver, H. Tegally, J.E. San, S.D. Shank, E. Wilkinson, A.G. Lucaci, J. Giandhari, S. Naidoo, Y. Pillay, et al., The emergence and ongoing convergent evolution of the SARS-CoV-2 N501Y lineages, Cell 184 (2021), https://doi.org/10.1016/j.cell.2021.09.003.
[138] W.T. Harvey, A.M. Carabelli, B. Jackson, R.K. Gupta, E.C. Thomson, E.M. Harrison, C. Ludden, R. Reeve, A. Rambaut, S.J. Peacock, D.L. Robertson, SARS-CoV-2 variants, spike mutations and immune escape, Nat. Rev. Microbiol. 19 (2021) 409–424, https://doi.org/10.1038/s41579-021-00573-0.
[139] Y. Cao, F. Jian, J. Wang, Y. Yu, W. Song, A. Yisimayi, J. Wang, R. An, X. Chen, N. Zhang, et al., Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution, Nature 614 (2023) 521–529, https://doi.org/10.1038/s41586-022-05644-7.
[140] C.Y. Tan, C.J. Chiew, D. Pang, V.J. Lee, B. Ong, D.C. Lye, K.B. Tan, Protective immunity of SARS-CoV-2 infection and vaccines against medically attended symptomatic omicron BA.4, BA.5, and XBB reinfections in Singapore: a national cohort study, Lancet Infect. Dis. 23 (2023) 799–805, https://doi.org/10.1016/S1473-3099(23)00060-9.
[141] C.-F. Team, Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis, Lancet (London, England) 401 (2023) 833–842, https://doi.org/10.1016/S0140-6736(22)02465-5.