Archives of Virology (2023) 168:148
https://doi.org/10.1007/s00705-023-05773-y

REVIEW

B lymphocytes in COVID-19: a tale of harmony and discordance

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Received: 7 January 2023 / Accepted: 29 March 2023 / Published online: 29 April 2023

Abstract

B lymphocytes play a vital role in the human defense against viral infections by producing specific antibodies. They are also critical for the prevention of infectious diseases by vaccination, and their activation influences the efficacy of the vaccination. Since the beginning of coronavirus disease 2019 (COVID-19), which became the main concern of the world health system, many efforts have been made to treat and prevent the disease. However, for the development of successful therapeutics and vaccines, it is necessary to understand the interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, and the immune system. The innate immune system provides primary and nonspecific defense against the virus, but within several days after infection, a virus-specific immune response is provided first by antibody-producing B cells, which are converted after the resolution of disease to memory B cells, which provide long-term immunity. Although a failure in B cell activation or B cell dysfunction can cause a severe form of the disease and also lead to vaccination inefficiency, some individuals with B cell immunodeficiency have shown less production of the cytokine IL-6, resulting in a better disease outcome. In this review, we present the latest findings on the interaction between SARS-CoV-2 and B lymphocytes during COVID-19 infection.

Keywords: B lymphocyte · B cell immune response · SARS-CoV-2 · COVID-19

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19), which was named by the World Health Organization (WHO) [1]. By April 16, 2022, more than 503 million cases with more than 6.2 million deaths had been reported globally, making COVID-19 the most fatal coronavirus disease [2]. The interaction between the spike (S) glycoprotein of SARS-CoV-2 and cells expressing angiotensin-converting enzyme 2 (ACE2) results in penetration of the host cell. SARS-CoV-2 mainly affects the respiratory system due to the predominant expression of ACE2 on the surface of type II alveolar cells of the lung [3].

Innate and adaptive immune system components, namely monocytes, neutrophils, dendritic cells (DCs), natural killer (NK) cells, macrophages, and T and B lymphocytes, are the most important mediators required to prevent and control SARS-CoV-2 infection [4]. However, uncontrolled immune responses resulting in lymphopenia and cytokine storm are the main pathophysiological attributes of COVID-19 [5].

B lymphocytes are important components of the humoral arm of the immune system and play a fundamental role in the adaptive immune response to viral infections through antibody-dependent and antibody-independent pathways [6, 7]. B lymphocytes can control viral infections by producing neutralizing antibodies and antibody-dependent cellular cytotoxicity (ADCC) responses [8]. In addition, these cells contribute to the elimination of viral infection and apoptosis of virus-infected cells through the production of effector molecules such as cytotoxic granzyme B (GrB) and lymphotoxin alpha (LT-α) [6]. On the other hand, immune alteration in B lymphocytes is the prominent characteristic of COVID-19 and is strongly associated with the severity of the disease [9]. It has also been documented that B cell defects are associated with a mild form of COVID-19, suggesting that B cells might contribute to inflammation and systemic production of inflammatory cytokines, especially

Communicated by Roman Pogranichniy

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interleukin (IL)-6 [10]. Hence, the aim of this review is to shed light on the importance of different types of B lymphocytes in SARS-CoV-2 infection as well as the role of B cells and their mediators in the development of vaccines to prevent COVID-19.

B Lymphocytes in COVID-19

B-1 cells

Recent studies have revealed the critical protective and immune-regulatory role of natural IgM secretion by B-1 cells in response to viral infection [11, 12]. It has been suggested that during an infection, B-1 cells initially egress from body cavities to accumulate in lymphoid tissues [13, 14]. These cells then begin to differentiate into antibody-producing lymphocytes, which are also capable of producing IL-10, which plays a protective anti-inflammatory role to control hyperinflammation [15].

It has been demonstrated that the production of IL-10 by B-1 cells reduces the production of pro-inflammatory cytokines and chemokines by macrophages and the influx of neutrophils into the lung [16]. Therefore, it is reasonable to presume that IL-10-producing B-1a cells may protect against the manifestation of acute respiratory distress syndrome (ARDS) in COVID-19 patients, as it potentially inhibits the production of reactive oxygen species (ROS), impairs macrophage activation, and prevents the formation of neutrophil extracellular traps (NETs) [17].

Single-cell RNA sequencing of blood samples from 10 COVID-19 patients in the early and late recovery stages showed a reduced number of B cells with superficial markers of human B-1 cells, and this was accompanied by decreased levels of IgM and IgD in serum [18]. Moreover, high-throughput immune profiling of 64 individuals showed that B-1 cell levels were decreased in COVID-19 patients [19]. Therefore, B-1a cells could potentially be beneficial for the treatment of COVID-19 due to their immunomodulatory effects.

Follicular B (B-2) cells

Follicular B cells, also known as B-2 cells, which have the most diverse B cell receptor (BCR) repertoire, are the subsets of B lymphocytes that are essential for the development of long-term T-dependent humoral immune responses [20]. These cells originate from bone marrow and can be found in the circulation and different lymphoid organs, including lymph nodes, intestinal Peyer's patches, and the spleen [21]. Naive follicular B cells activated by T-dependent antigens dynamically develop germinal centers (GCs) and undergo proliferation and differentiation into plasmablasts, plasma cells, or memory B cells [22].

Interaction between B-2 cells and activated $CD4^+$ T cells induces antibody production against most polypeptide antigens. The binding of activation-induced CD40 ligand on $CD4^+$ T cells to B-2-cell-expressed CD40 provides the essential help needed for the activation of B-2 cells in this interaction. This engagement, along with BCR stimulation by specific antigens, leads to the proliferation of B-2 cells. It also results in the expression of activation-induced cytidine deaminase (AID) and B cell lymphoma 6 (Bcl-6). AID and Bcl-6 are both necessary for class switch recombination (CSR) and affinity maturation (AFM) of the antibody variable sequence [23] .

Similar to what has been observed in SARS-CoV infection, BCL6-expressing B cells, follicular helper T (TFH) cells, and GCs have been found to be absent during the acute phase of SARS-CoV-2 infection [22] (Fig. 1). Single-cell V(D)J sequencing of samples from 12 convalescent COVID-19 patients revealed that the BCR diversity was significantly decreased and had more of a tendency to skew toward different V gene segments in these patients than in healthy controls. Moreover, IgG1, IgG3, and IgA1 isotypes were found at significantly higher levels in COVID-19 patients. Also, the CDR3 sequences of the heavy chain in clonal BCR in patients were more convergent than in healthy controls [24].

A study of 17 patients who had recovered from COVID-19 revealed that, in five individuals, the level of specific IgG decreased after 5–8 months. Also, SARS-CoV-2-specific IgG-producing B cells persisted in all patients upon *in vitro* differentiation of blood-derived B cells [25, 26].

B-2 cells play a potential role in the effective immune responses against SARS-CoV-2 and the elimination of COVID-19 infection. This suggests that the enhancement of follicular B cells might be favorable in the management of COVID-19.

Marginal zone B cells

These cells contribute to T-cell-independent immune responses, especially to capsulated bacteria, and may respond to these pathogens faster than follicular B cells through antibody production [27]. Upon stimulation of the intracellular and extracellular Toll-like receptor, marginal zone B cells leave the marginal zone and contribute to the IgM immune response [28]. It has been reported that marginal-zone-like, memory, and transitional B cells are reduced in moderate-to-severe COVID-19 infection [29].

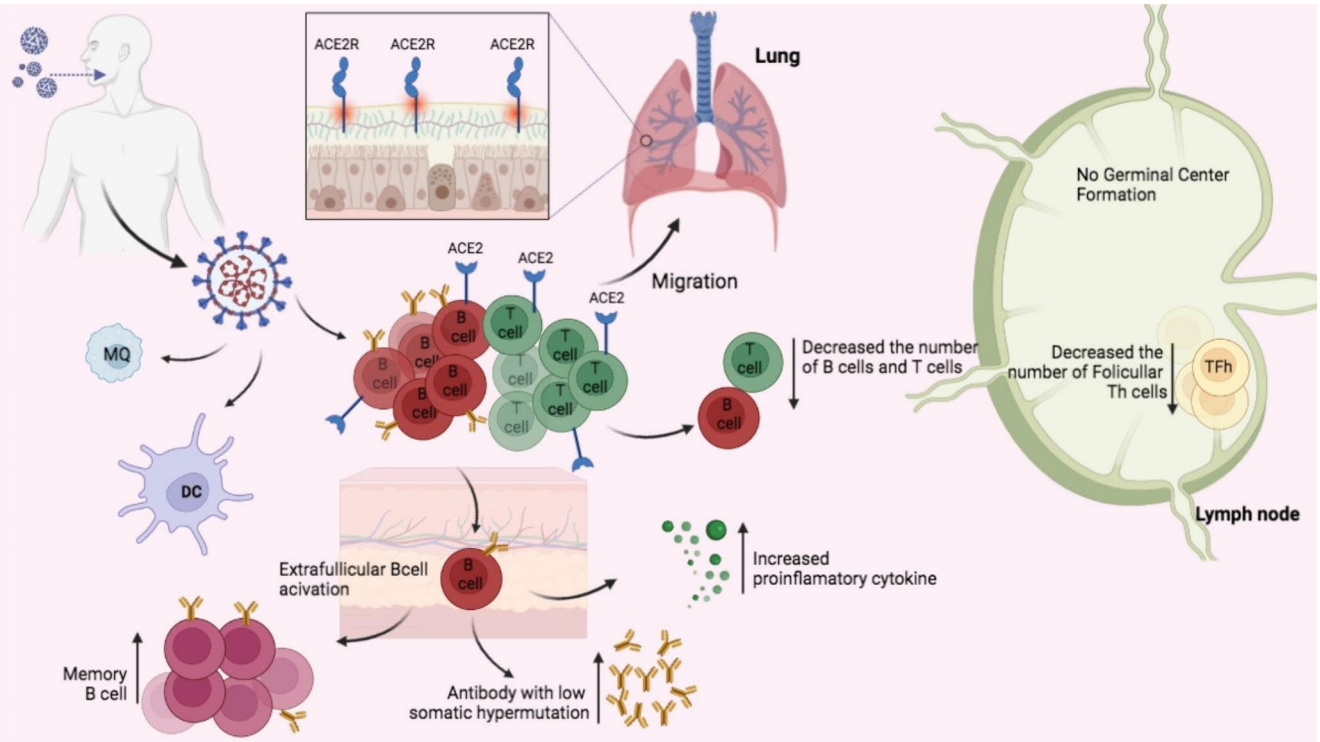

Fig. 1 B cell immune response in severe COVID-19. In severe COVID-19, the virus infects lymphocytes expressing ACE2 on their surface, causing depletion of T cells and B cells, and directly activated B cells migrate to lung tissue. Apoptosis and cell migration lead to a decreased number of B and T cells. Because of the decreased number of follicular Th cells, a germinal center is not formed, and extrafollicular B cell activation results in the production of antibodies with low somatic hypermutation and of proinflammatory cytokines.

Memory B cells

Memory B cells (MBCs) play an important role in the occurrence and severity of COVID-19 re-infection. They develop through GC-dependent or GC-independent pathways and are categorized into several subsets with distinct functions and cell surface biomarkers. In general, MBCs that develop without GC formation do not undergo class switching and affinity maturation and are not able to produce effective neutralizing antibodies (NAbs) against viral infections. Also, CD80-PD-L2-double-negative populations of MBCs, which develop through a GC-independent pathway and differentiate into antibody-secreting cells, have the potential to re-enter GCs for activation and development into antibody-secreting cells that produce high-affinity NAbs. During SARS-CoV-2 re-infection, MBCs are quickly activated and differentiate to into antibody-secreting cells. The majority of COVID-19 patients lack antigen-specific antibodies, which is similar to what is observed with SARS patients, in whom MBC responses are undetectable in 100% of recovered individuals 6 years after infection [30].

The number of switched memory B cells has been found to be decreased in COVID-19 patients, and this is independently associated with the mortality rate among these patients [31]. During primary SARS-CoV-2 infection, T cells help in the differentiation of B cells in the GC and mediate the induction of a large repertoire of MBCs. Patients with insufficient T cell help have poor GC reactions, fewer antigen-specific antibodies, and fewer switched MBCs, and they develop a severe form of the disease [31].

It has been demonstrated that immune alterations can occur in the biomarkers of memory B cells. For example, higher levels of T-bet and Fc-receptor-like 5 (FcRL5) are expressed by SARS-CoV-2-spike-specific memory B cells in patients with non-severe COVID-19 than in those with severe infection [32]. Moreover, memory B cells play a fundamental role in the rapid immune response to SARS-CoV-2 after vaccination [33].

Generally, the protection resulting from immune memory against coronaviruses is not able to persist for a long time or prevent reinfection. Numerous studies have been conducted on the evaluation of memory immune responses in COVID-19 re-infection. Monitoring the titer and duration of circulating antibodies in serum is the most common method for the assessment of B cell memory. One study showed that antigen-specific IgG levels persist for 3–4 months after infection, while IgA and IgG decline faster [34, 35]. In contrast, several other studies have demonstrated durability in immune memory. In one cohort study, receptor binding domain (RBD)- or nucleocapsid (N)-specific MBCs

were examined in 25 patients grouped as mild, moderate, or severe, and it was revealed that all groups had increased MBCs from the onset of disease to 150 days after infection [36]. Furthermore, RBD- or N-specific MBCs mostly possess IgM and IgG with different immunophenotypes, and the number of RBD-specific IgG MBCs correlates with the number of TFH cells. In the early stage of SARS-CoV-2 re-infection, IgM-secreting MBCs are dominant, but they decrease after 20 days as IgG-secreting MBCs continuously increase and become dominant and are detectable 120–240 days after symptom initiation. One long-term cohort study of 188 cases showed that circulating RBD-, N-, and spike (S)-specific MBCs could exist for more than 6 months and up to 8 months after the onset of symptoms. In addition, the majority of RBD-specific MBCs that increased over time from 1 month to 6 months after the onset of symptoms secreted IgG [37]. In another long-term study, the number of MBCs was assessed in mild cases, and it was revealed that IgG^+ MBCs persist and increase for 3 months after SARS-CoV-2 infection [38]. However, because of the limited number of re-infected study subjects and the lack of sufficient data, more research is needed to elucidate the role of MBCs in SARS-COV-2 re-infections [30].

Plasmablasts and plasma cells

After antigen recognition, B cells are activated and differentiate into plasmablasts and plasma cells, which play a fundamental role in antibody-dependent and antibody-independent immune responses [6]. In a study of 2301 adult patients with severe COVID-19, 16% of the patients had detectable plasma cells in their peripheral blood, which was associated with a higher survival rate [39]. Turner et al. demonstrated that S-specific long-lived bone marrow plasma cells (BMPCs) were still detectable in 18 patients 7 to 8 months after recovery from mild COVID-19 [40].

Despite the persistently elevated plasmablast numbers in acute SARS-CoV-2 infections, studies have shown that plasmablast numbers return to baseline levels in convalescent samples within 6 months after infection, indicating that these B cell subset changes are transient. Other B cell phenotypes including non-plasmablast $CD71^+$ activated B cells, $FcRL5^+/CD11c^+$ B cells, and a phenotype with intermediate characteristics have been reported in the acute phase of infection [41].

Alterations in blood B lymphocytes in COVID-19 patients

Changes in the number and phenotype of blood cells such as lymphocytes, monocytes, and macrophages have been reported in COVID-19 patients [42], with alterations in lymphocytes being the most notable [43]. Lymphopenia (absolute number of lymphocytes less than 1.0×10^9/L), which is the most common hematological anomaly in COVID-19 patients [44], is commonly observed at the beginning of the disease [45] and is seen in up to 85% of severe cases [44]. The presence of lymphopenia is usually considered a sign of a weak immune response to viral infection [44]. The correlation between lymphopenia and disease severity indicates that T and B cells play key roles in the pathology of COVID-19 [9] (Fig. 1). This association is accompanied by a threefold increase in the risk of developing a severe form of COVID-19 in lymphopenic patients [46].

Of the lymphocyte subtypes, B cells show the greatest difference between patients with COVID-19 and uninfected individuals, since B cells are responsible for humoral immunity through the production of antibodies [47]. B cells have been shown to exhibit a rapid increase in clonal expansion and diversification in response to SARS-CoV-2 infection [48], and the quality of the B cell response following SARS-CoV-2 infection defines the course and degree of protective immunity [9, 49].

Shifts in B cell subpopulations [45] in severe COVID-19 are correlated with disease course, severity of illness, clinical outcome, and survival rates [50, 51]. COVID-19 patients requiring intensive care showed especially low levels of total lymphocytes, B cells, CD4 T cells, and CD8 T cells [52]. However, it is still not known whether the lymphocyte count is predictive of the severity of COVID-19 [46, 48].

A decrease in the absolute number of lymphocytes might occur due to virus attachment and penetration into lymphocytes expressing ACE2 on their surface, causing depletion of both T cells and B cells (Fig. 1) or, less directly, due to immune injury caused by inflammatory intermediates such as inflammatory cytokines [44]. Although the underlying reason for lymphopenia in COVID-19 cases remains unknown, it has been suggested that the decrease in lymphocytes is due to apoptosis or invasive migration of lymphocytes from the peripheral blood to the lungs, where a high level of viral replication occurs [43]. Furthermore, SARS-CoV-2 infection may suppress the functions of lymphocytes for a long time [53].

In general, after viral infection, depending on the pathogen involved, alterations in absolute lymphocyte numbers and subsets vary. This implies a possible association between lymphocyte subset alterations and pathogenic mechanisms in viral infections [44, 45, 54]. The reported patterns of lymphocyte subtype changes in patients with COVID-19 are very diverse and controversial and need further investigation [55].

Interplay between B lymphocytes and innate and adaptive immune cells in SARS-CoV-2 infection

It is believed that the immune response to SARS-CoV-2 infection is initiated by the expression of type I IFN and related molecules following recognition of the virus by the innate immune system [56]. After binding to its receptors ACE2 and TMPRSS2 (transmembrane serine protease 2) on the cell surface, the virus is internalized, actively replicates, and is released from the cell by a process called "pyroptosis" which also results in the release of various damage-associated molecular patterns (DAMPs). Recognition of these DAMPS by neighboring cells triggers the generation of pro-inflammatory cytokines and chemokines [57–60]. Macrophages, monocytes, T and B cells, and other immune cells are attracted to the site of infection and establish a pro-inflammatory feedback loop. Macrophages and DCs cross-present antigens from apoptotic virus-infected epithelial cells and prime B cells and $CD4^+$ T cells [61].

During the immune response to SARS-CoV-2 antigens, B cells become activated and migrate to the lymph node, where they form GCs. As B cells migrate from the light zone to the dark zone, they compete for signals derived from T cells, including cytokines and CD40 ligands, which promote their migration [49] (Fig. 2).

Virus-specific $CD4^+$ T cells commonly differentiate into Th1 cells, which produce cytokines and have antiviral activity, and T follicular helper (Tfh) cells [62]. After infection, these cells migrate to the B cell follicle in response to the chemokine CXCL13, and by interaction with cognate virus-specific B cells in this site, they provide help signals and facilitate GC maturation [63] (Fig. 2).

In the dark zone, the extent of B cell division and somatic hypermutation depends on the level of T cell support received by B cells in the light zone. After returning to the light zone, B cells that have undergone productive mutations accumulate and present captured antigens to T cells, which facilitate their eventual differentiation into plasma cells and memory B cells [49] (Fig. 2). Due to a rapid increase in plasmablasts

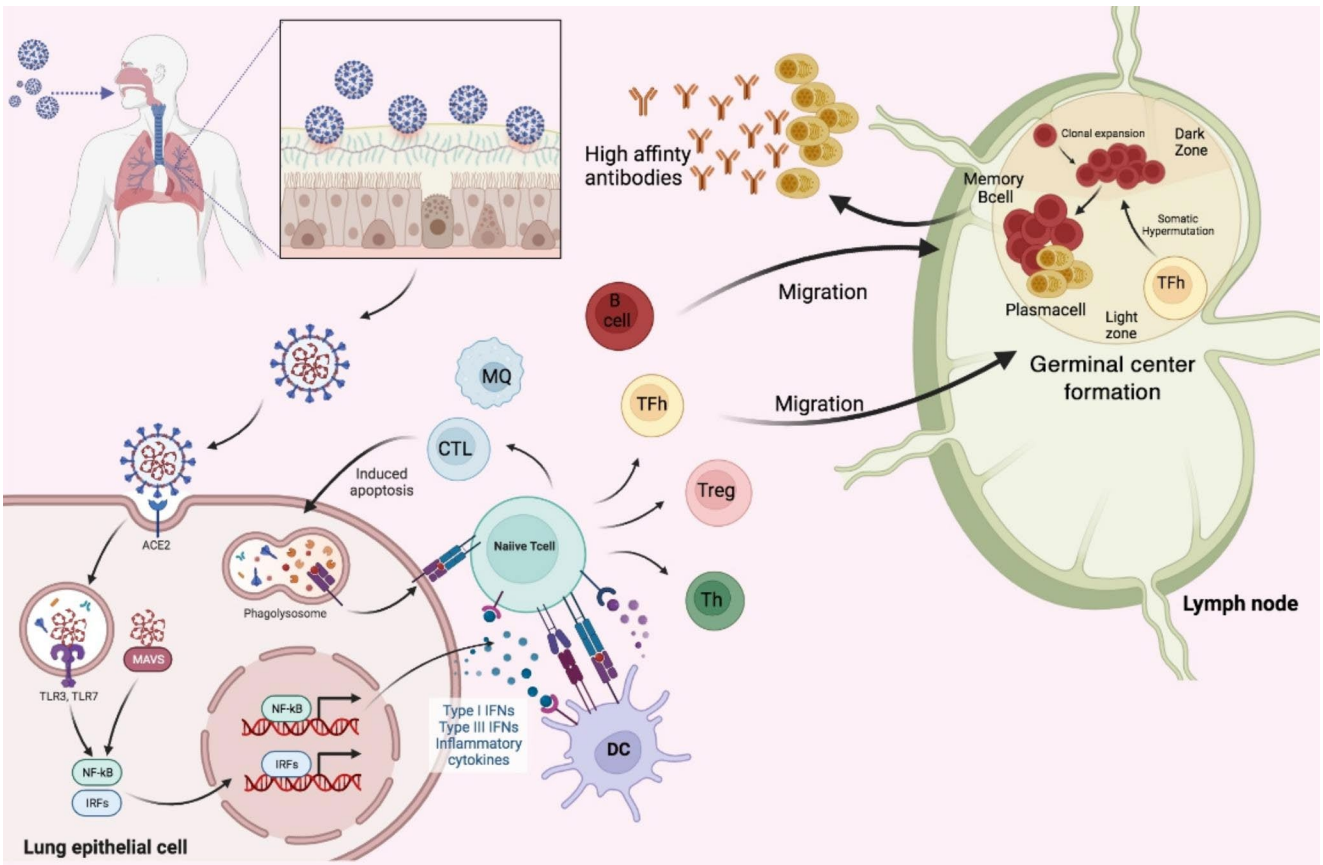

Fig. 2 B cell immune response in mild COVID-19. During the immune response to SARS-CoV-2 antigen, B cells become activated and migrate to the lymph node, where they form germinal centers (GCs). As B cells migrate from the light zone to the dark zone, they compete for signals received from T cells. Virus-specific $CD4^+$ T cells differentiate into T follicular helper cells (Tfh). These cells migrate to the B cell, and by interaction with cognate virus-specific B cells at this site, they provide help signals and facilitate GC maturation. The extent of B cell division and somatic hypermutation depends on the level of T cell support received by B cells in GCs. Eventually, B cells differentiate into high-affinity antibody-producing plasma cells and memory B cells.

during the early weeks of infection, high antibody titers are produced immediately after infection but decay very rapidly after that the infection has resolved, and this is followed by lower levels of antibody production by distinct populations of longer-lived plasma cells [64].

It appears that the interaction between SARS-CoV-2, Tfh cells, and antibodies is complex. Patients with severe COVID-19 have elevated levels of memory B cells and antibodies with low somatic hypermutation that fail to resolve the disease. This could be associated with a robust extrafollicular B cell response, an increase in pro-inflammatory cytokines, or a defect in the formation of functional GCs due to decreased numbers of Tfh cells in draining lymph nodes and the spleen (Fig. 1). However, in mild COVID-19 cases, there is robust somatic hypermutation, which results in the generation of high-affinity plasma cells derived from mature GCs (Fig. 2). It should be considered that impaired virus elimination could be due to impaired T-cell-mediated clearance of infected cells [49]. Humoral immunity depends on proper activation of B cells in connection with other immune cells, which allows them to differentiate into memory B cells and neutralizing antibody-producing cells, which produce antibodies that, together with complement factors such as C3a and C5a, tag viruses to be killed by phagocytic cells [65].

Antibodies in COVID-19

Studies have shown that most individuals develop a strong humoral immune response following SARS-CoV-2 infection [66, 67]. Wen et al. showed that, during the recovery period of COVID-19, examination of peripheral blood mononuclear cells (PBMCs) showed reduced levels of naive B cells, while the plasma cell count was markedly increased [68]. Serum antibody titers against SARS-CoV-2 vary in magnitude from individual to individual, but in almost all patients, they decline rapidly over the first 4 months, followed by a more gradual decline [69, 70]. In contrast, over the first 4 to 5 months after infection, the memory B cell response to SARS-CoV-2 increases and eventually reaches a plateau. According to Laidlaw et al., SARS-CoV-2-specific plasma cells are sustained in the bone marrow between 7 and 11 months after infection, which is consistent with a model in which long-lived bone marrow plasma cells maintain serum antibody levels for longer periods of time after infection [71]. Individuals with severe COVID-19 tend to have a stronger memory B cell response and a higher level of serum antibodies than individuals with milder infections. This could be attributed to the fact that patients with severe infection produce a large number of extrafollicular B cells and have elevated levels of neutralizing antibodies and inflammatory cytokines [69, 72]. The number of follicular helper T cells in the spleen and draining lymph nodes of patients with severe infection may be markedly decreased, as evidenced by their inability to form functional germinal centers. The results of the studies show that severe COVID-19 is associated with low levels of somatic hypermutation, which may reflect impaired germinal center responses. This may lead to the antibodies that are produced being ineffective in mediating disease resolution. It is also noteworthy that many individuals with severe COVID-19 have a robust circulating follicular helper T cell response, which suggests that the germinal center response is not defective in all cases [71, 73, 74].

In addition to triggering an early extrafollicular reaction, mild SARS-CoV-2 infection also induces activation of plasmablasts and memory B cells. Despite the near-germline sequences of early SARS-CoV-2-specific memory B cells, the mutations in their variable heavy genes suggest that these cells are part of a continuous process of the germinal center. Further evidence supporting this model can be found in the presence of long-lived plasma cells in the bone marrow of infected patients, since germinal centers are the source of high-affinity plasma cells [41, 75]. Compared to antibodies from memory B cells that developed at earlier time points, antibodies generated from somatically mutated SARS-CoV-2-specific memory B cells exhibit higher neutralizing breadth, neutralizing potency, and antigen-binding potency. There is an association between somatic mutations in the variable heavy gene of memory B cells followed by sustained antibody response and rapid recovery from infection [66, 70]. Furthermore, 10 months after infection, SARS-CoV-2-specific antibodies in the patient's serum show enhanced neutralizing activity. These data confirm that germinal-center-induced plasma cells and memory cells are necessary for the development of B cells that are capable of protection against SARS-CoV-2 infection, pointing to the essential role of the germinal center in the eradication of infection [76].

The average period of seroconversion for anti-RBD IgM, IgG, and IgA is between 5 and 15 days after the onset of symptoms, while in hospitalized patients, the seroconversion rates for these antibodies reach their maximum between 28 and 42 days after symptom onset [64, 77].

Although antibodies have been shown to neutralize viral particles, they can also kill infected cells, and this may be an important mechanism of action *in vivo* [78]. Currently, there is a lack of evidence that this occurs in human SARS-CoV-2 infections, but Fc-receptor-associated functions of antibodies in serum have been correlated with protective immunity in a SARS-CoV-2 non-human primate vaccine model, and antibodies that were able to bind to Fc receptors have also been found to be more protective in mice. Furthermore, individuals who failed to recover from COVID-19 infection

have been found to have fewer antibodies with Fc-dependent functions [79, 80]. Generally, a high antigen load correlates with higher antibody titers, and this is true in a wide variety of animal models. Similarly, in large cohort studies of COVID-19 disease severity, total spike antibody titers and neutralizing antibody titers were positively correlated with disease severity [81].

Neutralizing antibodies in COVID-19

The development of neutralizing antibodies (NAbs) against SARS-CoV-2 appears to be a fairly simple process, and it has been reported that many B cells can produce these antibodies with little or no affinity maturation needed [82]. Furthermore, the data suggest that SARS-CoV-2 neutralizing antibodies are typically produced by naive B cells rather than existing cross-reactive memory B cells. However, the titer of anti-SARS-CoV-2 neutralizing antibodies in circulation is relatively low in a substantial fraction of recovered patients [82].

The production of NAbs is positively associated with factors such as age, male gender, and disease severity [83]. Wu et al. found that the NAb titer was positively associated with the CRP (C-reactive protein) level and negatively associated with the lymphocyte count at the time of COVID-19 disease [84]. Notable differences in the duration and outcome of the disease have been observed between men and women, with males experiencing a longer disease duration and producing a higher titer of NAbs [83, 85, 86]. In addition, higher antibody levels have been observed in convalescent plasma from males than in that from females. This is a striking finding, given that females most often develop stronger immune responses than males do. One possible reason for the difference between males and females in the antibody responses to SARS-CoV-2 is that male COVID-19 patients tend to have a more severe form of the disease than female patients and that enhanced immune responses associated with greater disease severity could lead to more B cell recruitment and, consequently, increased antibody production [83].

One possible explanation for the positive association between NAbs and age is that elderly people do not respond to immune stimulation as robustly as the young. Therefore, elderly individuals develop a severe form of COVID-19 and have impaired B cell responses with high levels of antibody production.

Underlying health conditions (e.g., chronic and toxic stress associated with stigma and systemic inequalities, increased rates of certain comorbidities), substandard living conditions and poor work circumstances may help to explain differences in the immune response to SARS-CoV-2, the higher burden of illness, and the higher mortality rate of patients who belong to minority ethnicities [87].

In most patients with SARS-CoV2, variable titers of NAbs are detected between 14 and 20 days after recovery [85]. Vanshylla et al. reported that the IgG NAb response was considerably higher in elderly patients than in younger patients. Also, NAb activity was significantly higher in hospitalized patients than in outpatients with or without symptoms. Moreover, they showed that most patients with mild COVID-19 had neutralizing antibodies for up to 10 months after the onset of disease [88]. Suthar et al. found that antibodies against the RBD and SARS-CoV-2-neutralizing antibodies can be found in most patients about 8 days after the onset of symptoms [89].

According to United States Food and Drug Administration (FDA) guidelines, the recommended titer of target antibody in plasma used for passive transfer of antibodies from recovering COVID-19 patients is 160. Lee et al. found that the neutralizing activity of SARS-CoV-2 neutralizing antibodies in sera from recovered patients increased significantly after the onset of symptoms and peaked on days 31–35. At this time, a serum with a neutralization titer of 160 has approximately 93% neutralizing antibody with moderate activity and 54% with high activity [90].

Regulatory B lymphocytes in COVID-19

In general, the role of regulatory B (Breg) cells in viral infections can be related to their inhibitory effect on the effector cells of the adaptive immune system, such as $CD4^+$ and $CD8^+$ T cells, as well as to induction of other suppressor cells such as regulatory T cells [91]. These cells have been found to function primarily by producing inhibitory cytokines. Although significant studies have been conducted regarding the role of Breg cells in viral infections [91], this has not been investigated in the case of SARS-CoV-2.

The importance of IL-10 for the inhibitory functions of Breg cells in viral infections is such that this cytokine can be considered the executive arm of Breg cells [92, 93]. Many cells, including macrophages, T cells, and natural killer cells, can also secrete IL-10 [94, 95]. Recent studies have shown that the primary cells secreting this cytokine are Breg cells, and the secretion of this cytokine is strongly stimulated by Breg cells in viral infections [96, 97]. One of the most effective strategies of the immune system to fight viral diseases is associated with $CD8^+$ T cells, which can be inhibited by IL-10. Another function of Breg cells during viral infection is to regulate the immune response and to direct it to Treg cells [91]. Many studies have shown the ability of Breg cells to control immune responses by regulating Treg cells [92, 97]. The role of IL-10 in the development of Treg cells

is such that if IL-10 is blocked, the process of converting $CD4^+$ $CD25^-$ T cells to Treg cells stops [98].

Autoreactive B lymphocytes in COVID-19

In COVID-19, a change in the percentage of blood B cells and T cells might break down immunological tolerance and induce lasting autoimmune diseases [99].

Also, in severe COVID-19, an elevated antibody level is associated with increased activation of autoreactive B cells and autoantibody secretion than in mild disease [49]. Numerous studies have highlighted an association between COVID-19 and the development of autoimmune diseases such as Guillain-Barré syndrome, Kawasaki disease, antiphospholipid syndrome, and autoimmune cytopenia vasculitis [99]. The process of autoimmunity in COVID-19 is probably related to molecular mimicry and bystander activation of immune cells that recognize self-antigens as foreign antigens and trigger autoreactive immune responses in susceptible individuals [99].

The similarity between hexapeptide sequences of the SARS-CoV-2 virion and human protein sequences that are recognized by B cell paratopes can lead to organ malfunction. A hexapeptide sequence present in SARS-CoV-2 and human proteins is detected in the serum of patients with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis. Therefore the presence of this sequence in COVID-19 patients could trigger autoimmunity during and after infection [100].

Moreover, in COVID-19 patients, a variety of autoimmune-like signs, including autoreactivity and immune dysregulation, are associated with disease severity. Comprehensive analysis of data obtained from severe COVID-19 patients has provided some evidence for the clonal expansion of B cells, proliferation of plasmablasts, and expansion of autoreactive antibody-releasing cells weeks after infection as a consequence of long-term COVID-19 [101].

Some clinical studies have indicated that autoreactive immune diseases, including rheumatoid arthritis, psoriatic arthritis, and type 1 diabetes, can develop soon after SARS-CoV-2 infection [102]. Some studies suggest that viral epitopes of SARS-CoV-2 may activate autoreactive T and B cells that are associated with cytokine storm and other mediators triggering autoreactive responses [103].

Pre-existing autoantibodies against interferons have been detected in 10–15% of patients with severe COVID-19. Autoantibodies against type 1 interferons have been detected in patients treated with interferons and in patients with SLE, myasthenia gravis, and autoimmune polyendocrinopathy syndrome [102, 104]. Major autoreactive autoantibodies in patients with moderate to severe COVID-19, such as antiphospholipid, anticardiolipin, lupus anticoagulant, and beta2 glycoprotein antibodies, are associated with coagulation dysfunction, which causes blood clotting in the organs [105, 106]. Anomalous coagulation in antiphospholipid syndrome and in association with COVID-19 is characterized by the presence of antiphospholipid autoantibodies, which correlates with disease severity and thrombosis [102].

Alteration of B cell activation associated with COVID-19 after years of producing autoantibody may break down immune tolerance and result in autoimmunity. This suggests a potential mechanism by which SARS-CoV-2 infection contributes to the development of autoreactivity, either by a direct attack on cells or indirect stimulation of antiviral immune responses [103].

Studies have also suggested possible activation of autoreactive B cells in the GCs of lymphoid organs and by the extrafollicular route. Patients with severe COVID-19, when compared to those with mild COVID-19, have larger numbers of extrafollicular B cells that are susceptible to activation and maturation and capable of producing autoantibodies [102].

In addition, it has been shown that SARS-CoV-2 can stimulate generalized polyclonal autoreactive B cells to produce autoantibodies and target self-antigens. Similarly, studies have indicated that post-COVID-19 autoimmune diseases include multiple sclerosis, idiopathic thrombocytopenic purpura (ITP), Graves' disease (GD), Guillain–Barré syndrome (GBS), myasthenia gravis (MG), and systemic lupus erythematosus (SLE). In these cases, T cells activated B cells to produce autoantibodies and trigger immune-mediated disease [103, 105, 107].

The wide spectrum of autoimmune-like phenomena occurring during SARS-CoV-2 infection suggests that COVID-19 could represent a good example of coronavirus-induced autoimmunity. It would be useful to better understand the relationship between autoimmunity and the pathogenesis of COVID-19, and vice versa [103].

All seven types of human-infecting coronaviruses could potentially play a role in the pathogenesis of multiple sclerosis (MS) and other autoimmune diseases. Possible mechanisms include molecular mimicry and antibody production against coronaviruses present in the intrathecal and cerebrospinal fluid of MS patients [103]. More studies are needed to determine the molecular mechanisms and clarify the different aspects of autoreactive B cell and autoantibody production during and after COVID-19.

B cell immunodeficiency and COVID-19

A cohort study published by Babaei et al. in 2022 indicated a higher risk of death after COVID-19 infection in patients with primary immunodeficiency [108].

A number of clinical observational studies have evaluated the efficacy of passive immunization with high titers of pathogen-specific antibodies for clearance of SARS-CoV-2 [109–112]. For instance, infusion of hyperimmune plasma was associated with rapid clinical improvement in patients with X-linked agammaglobulinemia (XLA) [109, 110].

An observational study showed that, although two XLA patients recovered from COVID-19, they had a higher risk of developing pneumonia after the infection [113].

In comparison to patients with dysfunctional B cells due to common variable immunodeficiency (CVID), patients with agammaglobulinemia tended to have a milder form of COVID-19, a shorter duration of disease, and no need for treatment with IL-6-blocking medications [114]. Considering that B cells are a major source of IL-6, the lack of B-cell-derived IL-6 was speculated to have prevented systemic autoimmunity and inflammatory responses [115]. However, the critical role of B cells in the adaptive immune response against the virus should not be ignored, because the production of virus-specific neutralizing antibodies is also likely to be an important step in recovery from COVID-19.

In contrast to primary immunodeficiency, secondary immunodeficiency may be caused by agents that are not intrinsic to the immune system but cause dysfunction of the immune system [116]. For instance, aging, measles virus infection, bone marrow failure and malignancies, and medications can have a deleterious effect on immunity. The number of B cells decreases with age because the ability of hematopoietic stem cells (HSCs) to generate new B cells decreases. Furthermore, the diversity of the B cell repertoire decreases as a consequence of a decrease in the number of naive B cells ($CD27^-$; with few somatic mutations in immunoglobulin genes) and an increase in the number of memory B cells ($CD27^+$; with multiple somatic mutations) [117]. B cell lymphopenia, inhibition of lymphocyte proliferation, and a loss of memory B cells are observed in patients infected with measles virus, which would make them susceptible to other infections [26]. Bone marrow failure and B cell or plasma cell malignancies have also been associated with hypogammaglobulinemia and subsequent recurrent infections [118]. Glucocorticoids have been shown to induce apoptosis and suppress B cell activation, proliferation, and differentiation [119]. A decline in circulating B cells after administration of glucocorticoids has been suggested [119, 120]. Monoclonal anti-CD20 antibodies such as rituximab are known to globally deplete B cells by targeting the transmembrane protein CD20 and inducing apoptosis. Moreover, newer kinase inhibitors, such as ibrutinib, which was developed for treatment of chronic lymphocytic leukemia (CLL), target BCR signaling [121].

B-cell-depleting immunotherapies including administration of anti-CD20 seem to predispose the patient to SARS-CoV-2 infection and prolong the course of disease [122, 123]. Glucocorticoid therapy has also been reported to delay SARS-CoV-2 clearance [124].

Lung tissue injury due to SARS-CoV-2 infection was reported to be alleviated after treatment with convalescent plasma in a pediatric patient with juvenile myelomonocytic leukemia after hematopoietic stem cell transplantation [125]. Another study showed that administration of convalescent hyperimmune plasma to hematological patients after chemo-immunotherapy-induced immunodeficiency promoted alleviation of COVID-19 symptoms. In addition, a considerable reduction in the level of C-reactive protein (CRP), an indicator of systemic inflammation, further confirmed that passive immunotherapy can facilitate SARS-CoV-2 clearance [112]. Cinar et al. reported the promising potential of convalescent immune plasma in combination with anti-cytokine therapy in a COVID-19 patient with extremely challenging comorbidities, including active myeloid malignancy, disseminated tuberculosis, and kidney failure [126].

Conclusions

B cells play a fundamental role in the prevention of and recovery from COVID-19. The presence of Tfh cells and GC formation are needed to help B cells produce functional and neutralizing antibodies against SARS-CoV-2 at the early stages of the disease. A robust extrafollicular B cell response, an increase in pro-inflammatory cytokines, and a defect in the formation of functional GCs due to decreased numbers of Tfh cells in draining lymph nodes and the spleen are found in severe COVID-19. Therefore, T cell activation and Tfh development should be considered when developing vaccines or management strategies.

Also, there is a significant correlation between the severity of COVID-19 and lymphopenia, which might be related to lymphocyte apoptosis induced by SARS-CoV-2. Patients who are at risk of developing a severe form of the disease might benefit from treatment with monoclonal antibodies or convalescent sera during the early phases of the disease to inhibit lymphocyte infection and reduction. More studies are needed to achieve a better understanding of the interactions that occur between SARS-CoV-2 and adaptive immunity components such as Treg cells.

Authors' contributions Conception and manuscript design: R J. Collection of data: AHM, AA, MD, FK, ZS, AM, FLA, AR, MR, RF, FF,

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Declarations

Conflict of interest The authors declare that they have no competing interests.

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