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RESEARCH ARTICLE

EXPLORING THE CONNECTION BETWEEN B LYMPHOCYTES AND SARS-COV-2 PATHOGENESIS

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ABSTRACT

B lymphocytes are essential for the human body's fight against viral infections because they generate certain antibodies. Additionally, they are essential for the vaccination-based protection of infectious diseases, and the vaccination's effectiveness is impacted by their activation. Numerous attempts have been undertaken to cure and prevent coronavirus disease 2019 (COVID-19), which has emerged as the primary global health system concern. However, knowledge of the interaction between the immune system and the COVID-19 causal agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is essential for the development of effective treatments and vaccines. Even though, a primary and nonspecific defense against the virus is initially provided by the innate immune system, a virus-specific immune response is first produced within a few days of infection by B cells that produce antibodies. These B cells are then transformed into memory B cells, which offer long-term immunity, once the disease has resolved. We summarize the most recent research on the relationship between B cells and SARS-CoV-2 during COVID-19 infection and highlighted the B cells recognition, response and its activation against COVID-19 in this review. Therefore, the purpose of this study is to clarify the significance of B cell in SARS-CoV-2 infection as well as the function of B cells and their mediators in the creation of COVID-19 vaccines.

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INTRODUCTION

B cell response to COVID 19: The betacoronavirus SARS-CoV-2 is a member of the subgenus Sarbecovirus. The World Health Organization declared a pandemic on March 12, 2020, due to the SARS-CoV-2 virus's global spread and the thousands of deaths brought on by COVID-19 (Ali Taherinezhad, 2023). The ongoing respiratory disease outbreak that was recently given the name of Coronavirus Disease 2019 (Covid-19) is the most current danger to global health. The coronavirus family includes thousands of different viruses. Only six, however—229E, NL63, OC43, HKU1, SARS-CoV, and MERS-CoV, have been linked to mild to serious respiratory tract infections in people (Shabir Ahmad Lone, 2020). Due to Covid-19's strong homology (80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and significant mortality during 2002–2003, it was discovered in December 2019. (Koichi Yuki 2020). It was quickly determined that a novel coronavirus, structurally linked to the virus that causes severe acute respiratory syndrome (SARS), was the culprit (Sivakumar Nagaraju (2024). SARS-CoV-2 was thought to have first spread by a zoonotic transmission linked to a seafood market in Wuhan, China. Later, it was realized that transfer from person to person had a significant impact on the outbreak that followed. Coronavirus disease 19 (COVID-19), the name of the illness brought on by this virus, was deemed a pandemic by the World Health Organization (WHO). A lot of people have been impacted by COVID-19, which has been recorded in about 200 nations and territories. Approximately 1,400,000 cases have been documented globally as of April 7th, 2020, according to the Center for Systems Science and Engineering (CSSE) at John Hopkins University. (Koichi Yuki 2020). Although other organ systems are also affected, the respiratory system is where the ARS-CoV-2 virus primarily manifests itself. The original case series from Wuhan, China described symptoms associated with lower respiratory tract infections, such as fever, dry cough, and dyspnea. Additionally, we noticed headache, lightheadedness, widespread weakness, vomiting, and diarrhea. It is now commonly acknowledged that COVID-19's respiratory symptoms can range from hardly perceptible to severely hypoxic with ARDS. According to the Wuhan article described above, there was only a 9-day window between the start of symptoms and the onset of ARDS, indicating that the respiratory symptoms can worsen quickly.

This condition may also be lethal. Patients with severe illnesses have been dying more often all across the world. According to epidemiological studies, mortality rates are greater among the elderly population and significantly lower among children. There is currently no effective targeted therapy, and medical management is primarily supportive. (Miho Fujiogi 2020). Several medications, including azithromycin, lopinavir-ritonavir, remdesivir, and hydroxychloroquine, have been explored in clinical trials, but none of them have yet been shown to be a reliable treatment. Clinical trials are being used to test more treatments. Lockdowns and social exclusion have been enacted in many nations to stop the virus from spreading further. Here, we'll go through what we now know about COVID-19 and think about the underlying mechanism that might account for the varied symptomatology, paying particular attention to the differences between pediatric and adult patients. (Sophia Koutsogiannaki 2020).

What are B CELLS?: A subset of lymphocytes known as B cells produce highly specialized antibodies against pathogenic antigens, aiding the adaptive immune response. When B cells recognize a particular antigen on the surface of presenting cells using their B cell receptor, they become activated in vivo. There was a group of macrophages at the lymph node among these cells. A reservoir of a person's antigenic experience is represented by memory T and B lymphocytes and long-lived plasma cells. We can learn more about the human immune response and find correlates of protection by examining the specificity and function of these cells. Histology and immune-phenotyping are two methods that have been used to investigate the origin of human lymphomas. This research suggested a cellular origin for various lymphoma types, but the origin was frequently unknown. Sequence analysis of the variable-region genes of B-cell lymphomas provided a molecular method to investigate the origin of the tumors after it was discovered that germinal-center B cells and their progeny are characterized by somatic mutations of the genes for the variable region of the B-lymphocyte antigen receptor. (Ralf Küppers2014). The sub capsular sinus macrophage structure is momentarily disrupted by inflammation brought on by viruses and bacteria, which reduces antigen acquisition and B cell responses to secondary infections. White blood cells called B lymphocytes employ antibodies to identify and eliminate foreign intruders, even though B cells normally benefit the immune system.

COVID 19 PATHOGENESIS

Infections caused by viruses have always been a major medical concern. Currently, viral diseases of one kind or another affect billions of individuals on Earth. According to scientists from the entire World Health Organization, viral infections make up 80% of infectious diseases (Andijan2017). This year's coronavirus disease (COVID-19) outbreak caused by the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has reached unprecedented worldwide proportions (Nile SH, 2020). A serious global public health problem is COVID-19, a potentially lethal illness brought on by the SARS-CoV2 virus. Although the symptoms of SARS-CoV2 infection are initially less severe than those of SARS or MERS infection, the virus eventually progresses to a deadly condition of hyperinflammation and respiratory failure in humans, causing pneumonia. I. an asymptomatic phase with or without detectable virus; II. a non-severe symptomatic phase with upper airway involvement; and III. a severe, potentially fatal disease with hypoxia, "ground glass" infiltrates in the lung, and progression to acute respiratory distress syndrome (ARDS) with high viral load. To create effective treatments, it is crucial to comprehend how the SARS-CoV-2 virus harms the lungs. The COVID-19 pandemic has had a severe effect on global health. According to recent studies, people with COVID-19 suffer substantial oxidative damage to a variety of biomolecules (Katarzyna Lesiów M, 2023).

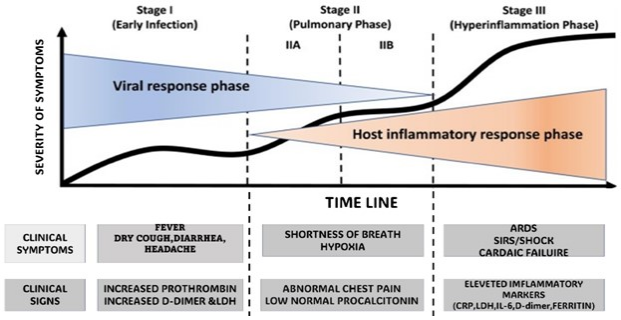

Figure 1. Illustration showing the severity of symptoms at various stages: First stage: early infection; Second stage: Pulmonary phase; Third stage: Hyper inflammation phase which shows high range of host inflammatory response (Planas D, 2021)

Spike (S), nucleocapsid (N), membrane (M), and envelope (E) are the four main proteins that the coronavirus genome encodes. The S protein is in charge of allowing the virus to enter the body's target ACEII-expressing cells. Both viruses use the angiotensin converting enzyme 2 (ACE-2) receptor to infect airway epithelial cells and endothelial cells; about 75% of the SARS-CoV2 genome is identical to the SARS-CoV genome, and the amino acid residues necessary for receptor binding are the same between these two viruses. The primary killer of COVID-19 disease is ARDS (acute respiratory distress syndrome), which also seems to generate immunopathogenic characteristics in SARS-CoV. The cytokine storm, an uncontrolled systemic inflammatory response brought on by immune effector cells releasing pro-inflammatory cytokines and chemokines, is one of the primary characteristics of ARDS. Patients with COVID-19 infection have been found to have high blood levels of several cytokines and chemokines, including: IL1-, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFN, IP10, MCP1, MIP1, MIP1, PDGFB, TNF, and VEGFA. In extreme cases of SARS-CoV-2 infection, which is comparable to SARS-COV, the accompanying cytokine storm sets off a strong inflammatory immunological response that contributes to ARDS, multiple organ failure, and ultimately death. Higher leukocyte counts, aberrant respiratory signs, and elevated plasma levels of pro-inflammatory cytokines were all present in COVID-19-infected patients. Acute COVID-19's direct cause of mortality is cytokine storm damage to the body's heart, kidneys, liver, and lungs, which results in multiple organ exhaustion. Shivraj Hariram Nile (2020)

B CELL RESPONSE TO VIRUS

A variety of cytokines and chemokines with antiviral and pro-inflammatory properties are released when viruses replicate in the respiratory tract (RT), triggering an effective virus-specific B and T cell response that aids in virus clearance. Most antibody-secreting cells (ASCs) in the upper RT secrete IgA, which has potent antiviral properties.

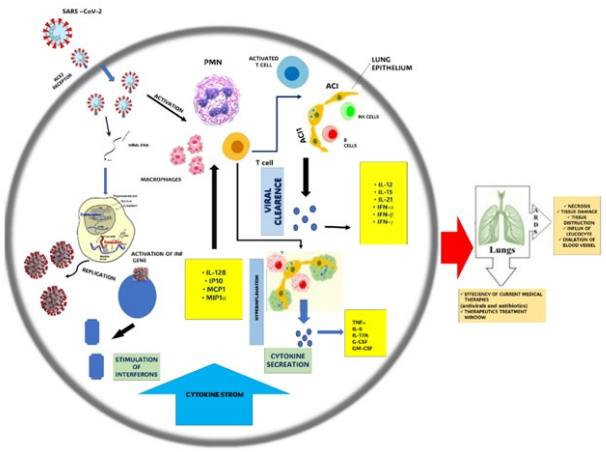

Figure 2. Schematic representation of COVID-19 pathogenesis and cytokine storm (Shivraj Hariram Nile, 2020)

B cell memory components are produced, which can offer defense against reinfection. Contrary to influenza infection, this condition led to a broad deficit in virus-specific IgA induction and a poor formation of B cell memory in the respiratory tract. According to the findings, characteristics of virus replication in the RT influence various components of the B cell response. An evolutionary adaptation of viruses that establish long-term latency and are periodically transferred after reactivation and shedding in secretions may be the B cell response. It is unclear what controls these B cell differentiation pathways, particularly when a virus is present in the RT. The current dissertation's findings indicate that host and virus-related variables play a role in controlling specific B cell response characteristics in the RT (Oran D.P, 2020). A key component of the immune system's defense against viral infections is the B cell response to a virus.

White blood cells called B cells are in charge of creating antibodies, which are proteins that recognize and combat particular diseases like viruses. Antibodies specific to a particular virus are essential for both preventing infection and speeding up the removal of the virus after it has taken hold. When a particular antigen is recognised, B cells divide and undergo differentiation to produce plasma cells, which are responsible for generating antibodies. A vital necessity for the best possible antibody responses is the appropriate assistance that CD4 T cells provide to activated B cells. This assistance is crucial for controlling antibody isotype switching in B cells, which is the process by which these cells go from expressing IgM to other isotypes (such IgG1, IgG2a, and IgA in mice) that have distinct functional properties. Furthermore, the assistance of cognate T cells is essential for activated B cells to take part in germinal center responses, which are the sites of affinity maturation of the antibody response and the generation of the biological components of B cell memory. These components include memory B cells, which produce antibodies quickly upon re-exposure to the same antigen, and long-lived plasma cells, which sustain high concentrations of protective antibodies.

B CELL RESPONSES TO ANTIGEN

Mature B cells recirculate between secondary lymphoid organs in search of antigen. Following cognate antigen encounter, B cells receiving T cell assistance can enter a few different developmental possibilities. First, the cells can undergo plasmacytic differentiation, form extrafollicular plasmablasts, and then form IgM secreting plasma cells. These cells are short-lived, do not have somatically mutated Ig genes, but they provide an immediate response to antigen. The second developmental possibility is the formation of a germinal center, a specialized structure where B cells go through cycles of proliferation accompanied by affinity maturation. This iterative process of Ig gene mutation and selection produces a B cell pool that can bind to antigen with the highest affinity. Class-switch recombination also occurs in the cells. Diversifying B cell responses and matching antibody function to immunological challenge are largely accomplished through immunoglobulin class flipping to IgG, IgA, and IgE. Exiting the GC are memory B lymphocytes and plasma cells with switched isotype BCRs that have undergone somatic mutation (Rebecca Newman, 2006).

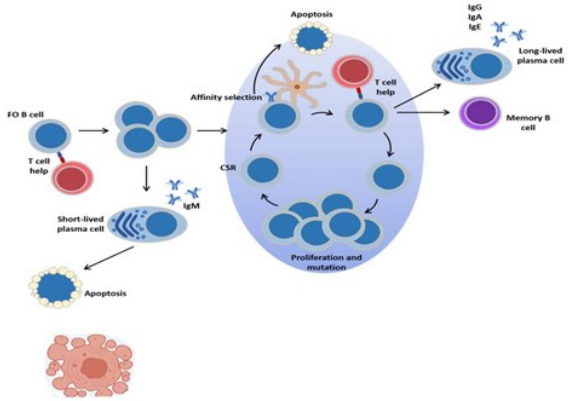

Figure 3. Illustration representing how a foreign antigen aids in recruiting, proliferating and producing plasma cells and memory cells from B cells (Rebecca newman2006)

B-CELL DEVELOPMENT

Two identical heavy and light chains are linked by disulfide bonds to form the immunoglobulins. The Ig heavy chain is first rearrange during B cell development, starting with D-J recombination, which happens in the common lymphoid progenitors (CLPs) and pre-pro) in large B cells. After that, V-DJ recombination produces a functional heavy chain protein (Ig pre-B cells), which is the next step. The recombined heavy chain then associates with the surrogate light chains and the dimer to form the pre-B cell receptor (pre-BCR) which is expressed on the cell surface. Ig Signalling through the pre-BCR drives intense proliferation and differentiation into the small pre-B cell stage. . Small pre-B cells that are dormant then undergo V-J rearrangement of the Ig light chain, resulting in the development of a fully functioning BCR with a distinct specificity that is expressed as IgM on the surface of immature B cells. Immature B lymphocytes are destroyed through a number of pathways in an effort to prevent autoreactivity when they come into contact with Ag that can cross-link their newly produced BCRs. Following their development in the bone marrow (BM), immature surface IgM+ B cells move to the spleen where they undergo two separate transitional B cell phases called T1 and T2, before converting into long-lived adult follicular and ovarian (FO) or marginal zone (MZ) B cells. As a result, the selection processes that B cells go through—both antigen-dependent and -independent ones—are closely controlled by signaling events. T3 B cells are a subpopulation of anergic B cells that have been chosen to diverge from the B cell developmental route; they do not produce mature B cells.

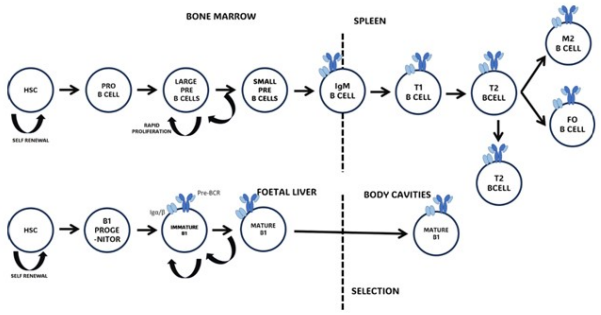

Figure 4. Diagram representing the selection of hematopoietic stem cells to mature B1 cell in the fetal liver with respect to body cavities and the HSC selection in bone marrow (Rebacca Newman; 2006)

A third population of mature B cells known as B1 cells exists in addition to FO and MZ B cells. Numerous tissues, such as the spleen, gut, peritoneal cavity, and pleural cavities, contain B1 cells. The fetal liver is where B1 cells' distinct haematopoietic origins may be found, and the embryo's initial wave of lymphopoiesis appears to be biased toward the development of B1 B cells. (Ali roghanian 2006)

B CELL RESPONSE TO PATHOGEN

Memory B (Bm) cell subsets, such as CD21+ resting, CD21-CD27+ activating, and CD21-CD27- Bm cells, are produced as a result of functionally specialized effector mechanisms used by B cells in response to various infections. These Bm cell subgroups' relationships with one another are still unknown. Here, we demonstrated that single coronavirus 2-specific Bm cell clones that cause severe acute respiratory syndrome infected patients exhibited flexibility in response to antigen pre-exposure. Early after severe acute respiratory syndrome coronavirus 2-specific immunization and after acute infection, CD21- Bm cells were the predominate subsets. CD21+ resting Bm cells were the predominant Bm cell subgroup in the blood at months 6 and 12 post-infection and were also seen in peripheral lymphoid organs, where they carried tissue residency markers. Single B cell clones can follow functionally distinct trajectories, as shown by the tracking of individual B cell clones by B cell receptor sequencing. Previously fated Bm cell clones were shown to be able to redifferentiate upon antigen rechallenge into other Bm cell subsets, such as CD21-CD27- Bm cells.

DEVELOPMENT

Every day, bone marrow produces millions of B lymphocytes that are sent to the periphery. In a tightly regulated series of processes, new B cells are produced quickly and continuously (LINDA L. KUSNER, 2023). The development of B cells from hematopoietic stem cells (HSCs) to mature B cells takes between one and two weeks, according to cell transfer experiments in which genetically marked donor HSCs are injected into unmarked recipients. Donor-derived mature B cells can be found in the recipient two weeks after HSCs are transferred into recipient mice. B-cell development starts with the asymmetric division of an HSC in the bone marrow and progresses through a number of progenitor stages that become increasingly more differentiated to produce common lymphoid progenitors (CLPs), which can give rise to either B cells or T cells. The majority of progenitor cells that remain in the bone marrow mature into B cells whereas those that move to the thymus to finish their development mature into T cells. (PatriciaM sikorski 2023)

ACTIVATION

A humoral immune response necessitates the proliferation and differentiation of antigen-activated naive B cells into high-affinity antibody-secreting cells in the specialized environment of the germinal center (GC), a process necessitating many metabolic requirements (SHARMA 2023) Activated B cells in germinal centers (GCs) or in extrafollicular locations engage in strong clonal growth. It has been demonstrated that proliferating lymphocytes engage in lactate dehydrogenase A (LDHA)-dependent aerobic glycolysis; however, the precise function of this metabolic pathway in a B cell's change from a dormant to a highly proliferative, activated state is still unclear (Woodruff2020).

B CELL RECOGNITION TO COVID 19

By screening of serum samples from COVID-19 convalescent patients using phage display of 12-mer random peptide libraries to identify SARS-CoV-2-specific B-cell epitopes . The pre-cleaned phage libraries were panned using COVID-19-serum-IgG-conjugated beads after the normal healthy donors' (NHS) sera were employed in a pre-screen to get rid of typical human IgG-bound phages. Following three rounds of biopanning, each phage clone was verified by ELISA screening, the DNA sequences of immunopositive clones were identified, alignment analysis was conducted, and B-cell epitope prediction was performed. . (Guo, JY., Liu, IJ., Lin, HT. *et al 2021*).

Here, we identify and report those that are 100% identical and contain no mutation in the available SARS-CoV-2 sequences (as of 21 February 2020) by examining the available experimentally determined SARS-CoV-derived B cell epitopes (both linear and discontinuous) and T cell epitopes. Therefore, there is a chance that these epitopes will trigger an efficient cross-reactive immune response against SARS-CoV-2. We concentrated specifically on the epitopes in the S and N structural proteins since they were previously found to produce a dominant and durable immune response against SARS-CoV-2. (Syed fazar ahmed 2020). Memory b cell reserves can produce antibodies that can protect against subsequent SARS-CoV-2 infections, however it is unclear if these antibodies can also protect against antigenically drifted variations. We analyzed memory B cell receptor-encoded antibodies against the SARS-CoV-2 spike (S) from 19 COVID-19 convalescent subjects, and we discovered seven significant antibody competition groups against epitopes that were consistently targeted by different people. (Tong Pei, 2021).

B CELLS RESPONSE TO COVID 19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)'s introduction into human populations in 2019 sparked the COVID19 global coronavirus pandemic, which has already begun to equal the extent and severity of the influenza pandemic of 1918. SARS-CoV-2 is believed to have originated as a zoonotic disease from a species of bat, possibly followed by various intermediate hosts, and possibly a period of covert human transmission. (Andersen *et al*., 2020; Zhou *et al*., 2020). A vaccination will likely be necessary to stop the COVID-19 pandemic while reducing mortality and the long-

term effects of illness, according to the rapid and extended transmission of SARS-CoV-2 and fading humoral immune responses, particularly after moderate infection. Recent regulatory approval and the start of mass vaccination campaigns in the US and other countries using lipid nanoparticle mRNA vaccines and adenoviral-vectored vaccines, each of which encodes the SARS-CoV-2 S, have sparked intense interest in the size, neutralizing titers, and duration of vaccine-stimulated antibody responses as well as in the effects on other immune cell types like T cells. The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) mRNA vaccines, which are administered intramuscularly in two doses, as well as the adenoviral vector Ad26.COV2.S (Janssen) vaccine, which is administered intramuscularly in one dose, are COVID-19 vaccines that are currently approved by the US Food and Drug Administration (FDA) for emergency use. After two doses of the mRNA vaccines, phase III studies revealed better than 90% efficiency at preventing COVID-19. (Baden *et al*., 2021; Polack *et al*., 2020) and 67% efficacy for Ad26.COV2.S (Sadoff *et al*., 2021). Other nations have authorized additional vaccines, such as the 70% effective ChAdOx1 nCoV-19 [vaccine chimpanzee (Ch) adenovirus-vectored vaccine (Ad), whose development was led by the University of Oxford (Ox)] (Voysey *et al*., 2021). All of these vaccines jointly target the SARS-CoV-2 S protein in an effort to raise viral neutralization titers, even though quantitative correlates of vaccine-mediated protection have not yet been shown.

One of the most significant findings from research on SARS-CoV-2 has been the extremely high efficacy of new mRNA-based vaccines. By the analyzed time points, 6 weeks and 4 months following the initial dosage, both the Pfizer-BioNTech and Moderna vaccines induce high levels of anti-S and anti-RBD IgG binding and neutralizing antibodies that gradually drop (Roltgen *et al*., 2021; Widge *et al*., 2021). Peak antibody responses are similar to those of COVID-19 patients who are very sick. (Ro ltgen *et al*., 2021). Intriguingly, compared to severe SARS-CoV-2 infection, serological responses to the PfizerBioNTech mRNA vaccine show a larger dominance of IgG over IgM and IgA isotypes, indicating effective IgG class flipping. This vaccine's antibodies also resulted in a narrower range of binding to other HCoV S proteins. It was hypothesized that the smaller antibody response seen after vaccination may be caused by distinct inflammatory conditions during infection versus vaccination as well as various anatomical compartments where immune responses are generated. (Roltgen *et al*., 2021). persons who were seropositive (due to a prior SARS-CoV-2 infection) responded to a single dose of the BNT162b2 or the mRNA1273 vaccine with post-vaccination IgG titers that were at least as high as those of seronegative persons following two doses (Krammer *et al*., 2021). A discussion about dose-sparing tactics and the quickest paths to herd immunity arises as a result of the majority of previously uninfected single-dose recipients mounting modest titers by day 21 in light of the scarcity of vaccinations in most nations. Initial analysis of the B cell populations induced by vaccination reveals that the frequencies of memory B cells created are roughly equal to those observed in COVID-19 survivors of severe illness (Wang *et al*., 2021b). In the upcoming months, further information will be needed to answer important issues regarding the longevity of vaccine-induced antibody titers for all SARS-CoV-2 vaccinations. Initial studies of titer declines in the months immediately following vaccination indicate that booster doses would be necessary to keep titers high enough to provide protection over the long term.

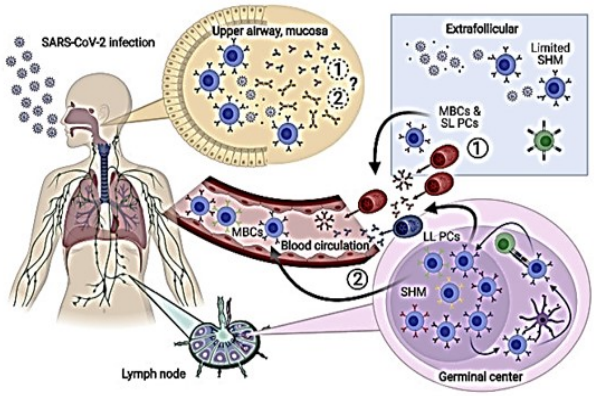

Figure: 5. Image showing the B cells involvement in COVID-19 infection and reinfection

When the SARS-CoV-2 virus invades, follicular T (Th) cells assist in activating naïve B cells. After T-B contact, B cells proliferate and differentiate quickly, resulting in the production of short-lived plasma cells (SLPCs), which produce early, low-affinity antibodies, and pre-germinal centre memory B cells (pre-GC MBCs). Long-lived plasma cells (LLPCs) and memory B cells (MBCs) are produced when other B cells reach the germinal centre (GC) to alter the structure through class-switching recombination (CSR) and boost antibody affinity by clonal expansion and somatic hypermutation (SHM). Both pre-GC MBCs and MBCs produced following GC reactions develop into plasma cells or produce a second GC in response to a second invasion or immunisation. Furthermore in a short period of time to produce high-affinity antibodies. Those B cells and antibodies secreted enter the blood circulation and peripheral tissues like mucosa to defend against viral infection and re-infection (Roltgen K, 2019).

CONCLUSION

B cells play a critical role in protective immunity against SARS-CoV-2, the virus that caused the coronavirus disease 2019 (COVID-19) pandemic, by secreting antibodies and modulating the humoral immune response. B lymphocytes are essential for both preventing COVID-19 and recovering from it. Early in the disease, T cells development aid in the production of functional and neutralizing antibodies by B cells against SARS-CoV-2. Thus, while creating vaccinations or management plans, T cell activation and development should also be taken into account. Furthermore, a noteworthy association has been observed between the intensity of COVID-19 and lymphopenia, maybe linked to the death of lymphocytes triggered by SARS-CoV-2. In order to prevent lymphocyte infection and reduction, patients who are at risk of developing a severe form of the disease may benefit from treatment in the early stages of the illness with convalescent sera or monoclonal antibodies. To have a better understanding of the interactions that take place between B cells and other components of adaptive immunity and SARS-CoV-2, more research is required. This review may enhance the comprehension of the relationship between B cells and SARS-CoV-2 and extend the horizons of future study for medical professionals and scientists towards developing a more potent vaccine targets.

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