Immune System Response to SARS-Cov-2

Madoui Soraya[1], Khither Hanane[1], Madoui Samia[2], Yekhlef Radhia[3] and Charef Noureddine[1]

[1]Laboratory of Applied Biochemistry, University Ferhat ABBAS Setif 1,19000, Algeria.

[2]Laboratory of human resources development. Ferhat ABBAS Setif1 University1,19000, Algeria.

[3]Research Center in Industrial Technologies CRTI, P.O. Box 64, Cheraga, 16014 Algiers, Algeria

E-mail: madoui.soraya@univ-sétif.dz /madoui_soraya85@yahoo.fr

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Abstract

SARS-CoV-2 related disease COVID-19 has caused more than 11 million infections and over 0.5 million deaths globally as of July 4, 2020.SARS-CoV-2 has spread globally, and many countries are experiencing ongoing local transmission despite various levels of control efforts.COVID-19 is primarily transmitted via respiratory droplets from an infected host. The virus primarily targets the upper and the lower respiratory tract and quickly disseminates to other organs. SARS-CoV-2 dysregulates immune signaling pathways which generate cytokine storm and leads to multisystemic disorders. The immune system is broadly divided into the innate immune system and the adaptive immune system. Although the adaptive and innate immune systems are linked in important and powerful ways, they each consist of different cell types with different roles.

Keywords: COVID-19, SARS-CoV, Immune system.

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I. Introduction

In the 1960s, coronaviruses (CoVs) were the first discovere. The CoVs cause mild respiratory and gastrointestinal infections in both humans and animals. In November 2002, an outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) was in Guangdong province, China. Then in 2012, it was the outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) in the middle eastern countries, especially in Saudi Arabia. These two outbreaks changed the concept

of coronaviruses infections. Both viruses have the exact origin and can transmit human-to-human or animal to human[1, 2].

In late December 2019, a similar outbreak of pneumonia-like respiratory diseases reported from Wuhan, Hubei Province, China, adding a new human CoV to the list.The World Health Organization [3] has officially called the novel Coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Virus Taxonomy (ICTV), and the condition caused by this virus COVID-19. SARSCoV-2 rapidly multiplies inside cells and stars the plethora of signaling cascade, from stimulating the pro-inflammatory response to antiviral response leading to cytokine storm. However, the pathogenicity of SARS-CoV-2 is notably less than SARS-CoV-1 and MERS-CoV, but its extreme transmissibility led to the pandemic, which resulted in the global lock-down and affected the global health scenario adversely [4].

The immune system is composed of organs that protect the body against diseases. It's crucial for maintaining health and preventing disease. It also safeguards the body against toxic substances, pathogens, and cell mutations (neoplasm) viruses, bacteria, fungi, protozoan, and worms and resists infections. There are two types of immunity areinnate immunity and adaptive immunity [5].

II. Innate immune response to SARS-CoV-2

The first line of defense against viral infection is innate immune signaling. Pattern-recognition receptors (PRRs) are located on the plasma membranes, endosomal membranes, and in the cytosol to recognize viral components or replication intermediates known as pathogen-associated molecular patterns (PAMPs). PRRs respond to viral PAMPs including lipoproteins glycoproteins and nucleic acids to initiate an antiviral response[6].

In the next sections, we'll explore at some of the processes that are increasingly being recognized as playing a role in COVID-19 immunopathogenesis, such as soluble components and interferon production when the virus reaches respiratory mucosal cells [7].

The S (spike) protein on the viral surface that interacts to the host cell receptor is heavily glycosylated in SARS-CoV-2: Angiotensin-converting enzyme 2 (ACE2) is a protein that converts

angiotensin II [8]. The stability of protein components, cell tropism, immunological detection, and camouflage of antigens identified by neutralizing antibodies can all be influenced by glycosylation of the viral surface. Distal mutations (10 nm away from the receptor-binding domain (RBD) may affect SARS-CoV-2 RBD-ACE-2 binding affinity, according to recent experimental findings. SARS-CoV-2 interaction to its receptor can be neutralized by targeting this polybasic cleavage site [9].

Antibodies found in nature. Anti-glycan antibodies, like naturally occurring ABO antibodies, are identified in serum without prior immunization. They are mostly of the IgM type, just as ABO antibodies. Natural IgM concentrations appear to reflect some of the clinical severity patterns observed in COVID-19 [10]. They drop dramatically with age (>40 years) and are found in lower quantities in men and those with blood group A. High anti-A antibody titers have been shown to protect against SARS-CoV-1 and a protective effect for SARS-CoV-2 has also been proposed. However, contradictory find has been observed. In a large multi-institutional patient cohort [11,12].

They find that individuals with blood type O have the lowest frequency of SARS-CoV-2 positive, but that blood type is not related with the probability of severe disease necessitating intubation or resulting in death. They discovered evidence for protective relationships between O blood groups and enrichment of B blood groups in SARS-CoV-2-positive patients in another investigation. Anti-A antibodies are in people of both the B and O blood groups, which contradicts this observation [13,14].

II.1. System of complements

The complement system is an important part of the innate immune response to viruses, butit can also cause proinflammatory responses. MBL (mannose binding lectin) is an innate immune complement system component that identifies mannose residues in the membranes of a variety of bacteria and functions as a soluble pattern recognition receptor. This identification stimulates the complement system, causing inflammation and increasing phagocytosis [14]. MBLis shown to bind SARS-CoV, causing C4 deposition in the virus and, in experimental models, limiting the virus's ability to infect [11]. Because of the presence of mannose-rich glycans in the S1 region of

SARS-CoV-2, it has been proposed that glycan recognition and binding to MBL may block S1-ACE interaction[8]. SARS-CoV risk has also been linked to some MBL genetic variants associated with decreased serum MBL levels. MBL levels in the blood are shown to decline with aging [15].

II.2. Cytokines

Interferons and other cytokines are various forms of cytokines that are produced by the body. In the fight against viruses, the IFN response is a critical initial line of defense. IFN types I and IIIappear to have a role in limiting infection [13]. For many respiratory viruses, including SARS-CoV-1, by creating a cellular state of viral resistance and initiating adaptive immune responses [16].

Following contact between microbial derivatives and cellular PRRs, IFN types I and III are transiently generated in cells. Nuclear factor kB (NF-kB) transcription and activation, as well as interferon regulatory factors, are activated by this interaction. Proinflammatory cytokines and type I and III interferons are produced in response to this activation. IFNs enhance the production of IFN-stimulated genes via the JAK-STAT signaling pathway [16]. Two defense pathways derive from these mechanisms: cellular antiviral resistance and cell attraction via the synthesis of various chemokines. These lines of defense are known to be countered by viral escape mechanisms based on the development of genetic resistance traits [17,18].

II.2.1. Interferons (IFN)

Type I interferons (IFN-α/β) are the initial line of defense against viral infection, promoting viral resistance in both infected and surrounding cells (autocrine action) by interfering with viral and cellular replication. A dysregulated inflammatory response has been observed in SARS-CoV-1 and MERS-CoV infections that cause acute respiratory disease, with delayed generation of type I IFN favoring the buildup of inflammatory monocyte-macrophages [19]. Recent evidence also suggests that the response to SARS-CoV-2 may be dysregulated in terms of types I and III interferons. SARS-CoV-2 infections cause very low IFN I and IFN III expression, as well as a limited response from IFN-stimulated genes, but normal expression of chemokines and proinflammatory cytokine genes, according to transcriptome profiles of diverse cell types [18, 20].

Neutralizing autoantibodies against type I IFNs (mostly IFN- α2 and IFN-ω) have recently been proposed as the cause of 10% of life-threatening COVID-19 pneumonia cases. The dynamics of type I IFN during SARS-CoV-2 infection are yet unknown, and more research is needed to determine whether IFN production is already lowered at the outset of infection or if it is delayed or exhausted after an initial peak [21, 22].

Another member of the IFN innate immunity family, type III IFN lambda (IFN λ) (IL-28/IL-29), has homologies with type I IFN and IL-10. Type III IFN expression is more limited than type I IFN expression and occurs mostly on mucous (respiratory and gastrointestinal) barriers. Type I and type III IFNs differ primarily in the expression of their receptors [23]: type I receptors are found in almost all cells, whereas type III receptors (the complex IFNLR1/IL10RB) are only found in epithelial cells, neutrophils, and certain activated immune cells (dendritic cells, macrophages, and B cells). This shows that type III IFNs play a more specific role in the mucosal immune response and adaptive response control [24]. Type III IFNs play a unique function in pulmonary immune responses because they are elicited sooner and with a lower viral load (than type I IFNs), and they inhibit the virus's initial dissemination and transmission from the upper respiratory tract to the lungs. They lack the proinflammatory characteristics of type I IFNs and may even have anti-inflammatory and tissue-protective properties [13,25].

According to recent discoveries from animal models of SARS-CoV-2 infection, types I and III IFNs contribute to restricting local (type III) and systemic (type I) viral spread [26]. However, they also imply that type I IFNs may cause a significant systemic and pulmonary inflammatory response. SARS-CoV-2 does not trigger a robust IFN I / III response (at least at lower viral loads), but does induce robust production of chemokines capable of recruiting inflammatory cells according to their recent study of transcriptional responses to SARS-CoV-2 compared to other respiratory viruses (Influenza A and SARS-CoV-1 [20]. They also observed considerable increase of monocyteand neutrophil-associated chemokines (CCL2, CCL8, CXCL2 and CXCL8, respectively) in various experimental models, which comprised pulmonary cell lines, animal models, and ex *vivo* samples (lung tissue from COVID-19 patients). Their findings are in line with data from COVID-19 patients who have peripheral neutrophilia, a predictive biomarker, and a predominance of peripheral-derived lung macrophages in the most severe instances [27,28].

Host age appears to influence cytokine profiles in the same sense as intrinsic viral suppression of IFN responses does), suggesting that the imbalance between proinflammatory cytokines and IFN production that occurs with aging may have substantial pathogenic implications in COVID-19 [16]. COVID-19 severity and consequences are closely related to age, with those over 65 accounting for 80% of all hospitalizations and having a 23-fold higher risk of death than those under 65. Cardiovascular disease, diabetes, and obesity all raise the chance of death from COVID-19, but they don't explain why age is an independent risk factor [29,30]. The immune system, like other organs and tissues, ages and undergoes two types of changes: immunosenescence and inflammaging. Immunosenescence is a progressive loss of immune function that impairs pathogen detection, alarm signaling, and clearance, increasing susceptibility to infections and other immune-relate chronic diseases such autoimmune illnesses and cancer[31, 32]. Inflammaging, on the other side, is a rise in systemic inflammation cause by an overactive but ineffective alert system, in which a decline in cellular repair mechanisms leads to an accumulation of genome and proteome damage, resulting in systemic immune changes and increased production of proinflammatory cytokines [5].

II.2.2. Interleukine

Another significant cytokine linked to inflammation and innate immunity is IL-1. It's produced mostly by active mononuclear phagocytes and can activate the production of other proinflammatory cytokines including IL-6 and TNF [29]. Although moderate dosages of IL-1 can be beneficial, excessive amount produced during a disease can be harmful. SARS-CoV-2 activates IL-1, which then increases the release of IL-6 and TNF, a proinflammatory combination that can cause a cytokine storm with potentially fatal lung and systemic consequences [33]. In addition to engaging in traditional generic inflammation, IL-1 and related cytokines (IL-33, IL-18) now appear to regulate innate immunity and inflammation in response to various microbial or environmental stressors. IL-1, for example, is involved in the development and polarization of innate lymphoid cells (ILC-3/Th17) [34].

II.3. Neutrophils

Neutrophils are immune cells. SARS-CoV-2 infection generates CXCL2 (GRO β) and CXCL8 (IL-8) chemokines, which are both neutrophil-recruiting chemokines, suggesting that neutrophils

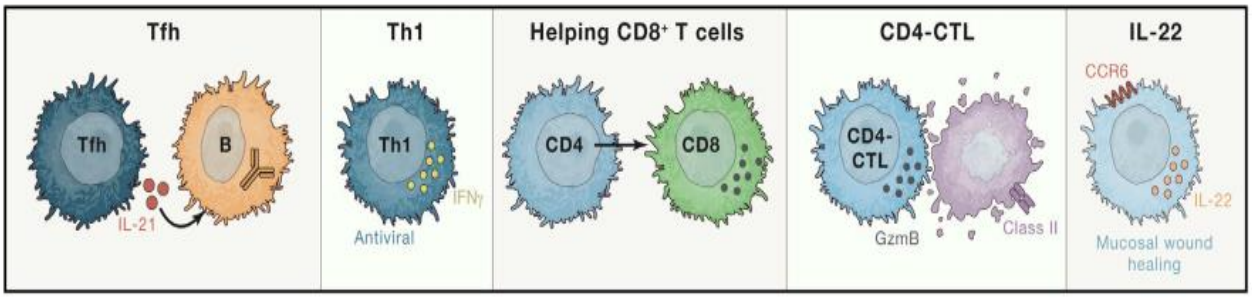
may be involved in the pathogenesis of COVID-19 [20]. This notion is supported by COVID-19 patients' distinctive peripheral neutrophilia [27, 28]. The neutrophil-to-lymphocyte ratio has been discovered as an independent risk factor for severe illness and death [29, 30]. Some researchers believe neutrophils play a role in the inflammatory response to COVID-19 by increasing organ injury and coagulopathy (immunothrombosis) through direct tissue infiltration and the creation of neutrophil extracellular traps (NETs), a process known as NETosis [35, 36].

PPRs or chemokines activate neutrophils, resulting in the release of NETs, which are extracellular webs of DNA, histones, microbicidal proteins, and oxidative enzymes. NETs may have a double-edged-sword effect, according to a growing body of studies [37]. While NETs have microbicidal function, their continued creation can cause a cascade of inflammatory reactions that harm surrounding tissues, promote microthrombosis, and result in permanent organ damage in the pulmonary, cardiovascular, and renal systems [38, 39]. In an autopsy research, revealed that circulating neutrophils were infected with SARS-CoV-2 and emitted large quantities of NETs in plasma, tracheal aspirate, and lung tissue specimens from COVID-19 patients. The findings imply that neutrophils are involved in the innate immune response to SARS-CoV-2 infection, and that NET-related necroinflammation is likely a key factor in the cytokine storm, sepsis, and multiorgan failure seen in COVID-19 [38].

III. Adaptative immune response to SARS-CoV-2 infection

In response to SARS-CoV-2 infection, humans produce SARS-CoV-2-specific antibodies, CD_4^+ T cells, and CD_8^+ T cells [40]. T cells, CD_4^+ and CD_8^+ T cells have a critical antiviral role through promoting the secretion of pathogen-specific antibodies by inducing Tdependent B cells and killing the virus infected cells, respectively [40, 41]. Virus-specific CD_4^+ T cells are important for complete virus clearance, controlling the virus replication and disease severity, virus-specific memory CD_8^+ T cells have significant role in host protection by multiple cytokines (IFN-γ, TNF-α and IL-2) and cytolytic molecules (granzyme B) production [42].

III.1. CD_4^+ T cells functions CD_4^+ T cells can develop into a variety of helper and effector cell types, including the ability to instruct B cells, assist CD_8^+ T cells, stimulate innate cells, have direct antiviral capabilities, and facilitate tissue repair (Fig. 1). Virus-specific CD_4^+ T cells regularly differentiate into T helper type one (Th1) cells and T follicular helper cells (Tfh) [41]. Th1 cells have antiviral activities due to the production of interferon gamma (IFNg) and other cytokines. Tfh cells are the specialized suppliers of B cell assistance and are essential for the development of



most neutralizing antibody responses, as well as memory B cells and long-term humoral immunity [43].

Fig. 1: CD_4^+ T cell functions observed in COVID-19 [41]

During an acute SARS-CoV-2 infection, circulating Tfh cells (cTfh) are produced that are specific to the virus. SARS-CoV-2 memory cTfh cells are also generated. Although neutralizing antibody titers have not been linked to a reduction in COVID-19 severity, SARS-CoV-2 cTfh cell frequencies have been linked to a reduction in illness severity. Notably, a significant proportioof SARS-CoV 2 cTfh is CCR_6^+, which may indicate mucosal airway homing, as has been reported for the common cold coronavirus HKU1(human coronavirus)[43, 44].

CD_4^+ T cells not only assist antibody responses, but they also assist CD_8^+ T cell responses. Although the precise CD_4^+ T cells helping CD_8^+ T cells remain unknown, interleukine-21 (IL-21) is crucial for CD_4^+ T cell help to CD_8^+ T cells, and IL-21 is a typical cytokine of TFH cells[11]. Despite supporting B cells and CD_8^+ T cells being key tasks of CD_4^+ T cells, CD_4^+ T cells may also develop into effector cells with more direct anti-pathogen activity, such as Th1 cells. IFNg+ CD_4^+ T cells protect mice from lethal SARS-CoV infection. IFNg is the main cytokine generated by SARS-CoV-2-specific CD_4^+ T cells from COVID-19 patients [40], with a distinct IFNg, TNF, and IL-2 protein profile of canonical Th1 cells [44].

CD_4^+ T cells with cytotoxic activity (CD_4-CTLs) are comparable cell types with direct cytotoxic activity that are linked to protective immunity against a variety of acute viral infections. Although the cytotoxicity degranulation marker $CD_{107}$was detected on SARS-CoV-2-specific CD_4^+ T cells, there was no evidence of a CD_4-CTL transcriptional signature [33]. One role of CD_4^+ T cells is to recruit additional effector cells to the location of the viral antigen, and gene production of CCL3/4/5 (MIP-1 s) and Chemokine (X-C motif) ligand 1 (XCL1) chemokines by SARS-CoV-2-specific CD_4^+ T cells may contribute to effector cell recruitment [43]. CCR_6 is a chemokine receptor that is linked to migration to mucosal tissues. CCR_6 expression by a fraction of SARSCoV-2-specific CD_4^+ T cells may indicate underlying Th17 characteristics. Nevertheless, undetectable or low levels of IL-17a protein expression have been described [33, 45].

IL-22, on the other hand, which may also be produced by mucosal CD_4^+ T cells, appears to be strongly expressed by SARS-CoV-2-specific CD_4^+ T cells.In some infections, CCR_6^+ IL-22 and CCR_6^+ IL-17 cells can function independently [40]. Notably, IL-22 is strongly associated with tissue repair, particularly of lung and gut epithelial cells, suggesting that the SARS-CoV-2 CD_4^+ T cell response may actively participate in lung tissue repair during COVID-19. SARS-CoV-2 memory CD_4^+ T cells appear to retain the capacity to make IL-22 [44].

III.1. 2. CD_8^+ T cells

Because of their capacity to destroy infected cells, CD_8^+ T lymphocytes are essential for viral infection clearance in many cases. The presence of virus-specific CD_8^+ T lymphocytes has been associated with enhanced COVID-19 outcomes in SARS-CoV-2 infections [44]. Overall, circulating SARS-CoV-2-specific CD_8^+ T cells are less consistently observed than CD_4^+ T cells. Predicted HLA class I epitope peptides can identify a significant proportion of the SARSCOV-2-specific CD_8 T cell response [40]. SARS-CoV-2 CD_8^+ T cells recognize a variety of SARSCoV-2 antigens, including Spike, nucleocapsid, M, and ORF3a [44].

SARS-CoV-2-specific CD_8^+ T cell responses, like SARS-CoV-2-specific CD_4^+ T cell responses, can develop quickly during acute COVID-19 [44], with a report of virus specific CD_8^+ T cells as early as day 1post-symptom onset PSO. SARS-CoV-2-specific CD_8^+ T cells in acute COVID-19 display large amounts of molecules associated with strong cytotoxic effector activities, including IFNg,

granzyme B, perforin, and CD107a. The expression patterns of memory SARS-CoV-2 CD_8^+ T cells are comparable [40].

III.1. 3. Antibodies and B cells

IL-6 and TNF cooperate at different levels in the regulation of B cell life and activity and act sequentially in B cell mediated immune response. The vast majority of SARS-CoV-2 infected patients seroconvert between 5-15 days PSO, with 90 percent of seroconversion by day 10 PSO [32].

Severe covid19 is characterized by an increase in proliferating, metabolically hyperactive, plasmablasts (PBs) and relative decrease in memory B cells, these changes coincided with severity of inflammation and disappeared with convalescence [47].

The Spike and nucleocapsid proteins are the main antigens studied for seroconversion. The titers of nucleocapsid and Spike immunoglobulin G (IgG) are tightly correlated. Spike is the target of SARS-CoV-2 neutralizing antibodies, and Spike's receptor binding domain (RBD) is the target of more than 90% of neutralizing antibodies in COVID-19 patients [46], with some neutralizing antibodies targeting the N-terminal domain instead (NTD). Spike IgG, IgA, and IgM antibodies develop concurrently in infected patients. Most SARS-CoV-2-infected patients produce neutralizing antibodies quickly, at the same time as seroconversion. B cells with a diverse set of heavy chain and light chain V genes generate neutralizing antibodies [48].

Neutralizing antibodies against SARS-CoV-2 show minimal to no somatic hypermutation. Overall, these findings indicate that developing neutralizing antibodies against SARS-CoV-2 is rather simple, since it can be achieved by a huge proportion of B cells with little or no affinity maturation [34]. The findings also show that SARS-CoV-2 neutralizing antibody responses are often generated by naïve B cells rather than pre-existing cross-reactive memory B cells [49]. Therefore, neutralizing epitopes on the SARSCoV-2 RBD domain, particularly those matched to the ACE2 receptor binding footprint, appear to be highly immunogenic and easily spotted by antibodies [42]. However, circulating SARS-CoV-2 neutralizing antibody titers are very low in a significant proportion of recovered COVID-19 patients, indicating that either the neutralizing antibody potency or serum concentration is suboptimal in this subgroup. Although it has now

been stated that antibodies may halt viruses outside of cells, antibodies may also destroy virally infected cells, which can be an essential mode of action in vivo [50].

The relationship between neutralizing antibodies, Tfh cells, and COVID-19 disease severity appears to be complicated. High neutralizing antibody titers are related with severe illness and perhaps extrafollicular B cell responses, whereas SARS-CoV-2-specific Tfh cells show varied connections depending on the research [43].

IV.Triggering innate and adaptative responses by vaccination

To stimulate adaptive immunity, a vaccine requires a pathogen-specific immunogen as well as an adjuvant. The latter activates T cells by stimulating the innate immune system and providing the second signal required for T cell activation [47]. An ideal adjuvant promotes innate immunity while avoiding systemic inflammation, which can cause serious side effects. Because of the intrinsic immunostimulatory characteristics of RNA, mRNA vaccines can function as both an immunogen (encoding the viral protein) and an adjuvant. Single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) are detected by several endosomal and cytosolic innate sensors upon entrance into cells, and these sensors are an important element of the innate immune response to viruses [34].

Endosomal Toll-like receptors (TLR3 and TLR7) attach to ssRNA in the endosome, while inflammasome components like MDA5, RIG-I, NOD2 and PKR bind to ssRNA and dsRNA in the cytosol, prompting cellular activation and the generation of type I interferon and numerous inflammatory mediators [24]. The latest vaccines contain purified, in vitro-transcribed single-stranded mRNA with modified nucleotides to decrease binding to TLR and immunological sensors, reducing type I interferon generation and its negative effect on cellular translation [19].The LNP carrier protects the mRNA even more, allowing it to be delivered to lymphatics and promoting protein translation in lymph nodes (LNs). The LNP is swallowed by dendritic cells (DCs) in the LN, which then produce and deliver the antigen to T cells for adaptive immune response activation [51].

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