

Coronavirus (COVID-19) and the Human Immunity: A Review

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Abstract. The coronavirus (COVID-19) exhibits a wide diversity of clinical manifestations due to the close association between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host immune mechanisms. SARS-CoV-2 viral clearance counts on adaptive immune responses, while innate immune populations such as dendritic cells (DCs) and macrophages have crucial roles in killing infected cells. Innate immune cells have vast pattern recognition receptors to induce different signaling pathways. Adaptive immune populations, including helper T cells (CD4+ T lymphocytes), cytotoxic T cells (CD8+ T lymphocytes), and B lymphocytes (sources of antibodies), can control infectious viruses to protect human bodies. In this review, how do the innate and adaptive immune systems recognize and respond to the invasion of the SARS-CoV-2 will be discussed.

1. Background

The COVID-19 pandemic began in December 2019 due to the spread of SARS-CoV-2 virus as a novel pathogen which was first identified in Wuhan, China. Since then, over 608 million cases of COVID-19 were confirmed and 6.5 million people had lost their lives till 17th September 2022 [1]. SARS-CoV-2 belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus* [2]. The causative pathogen enters the host cells through the functional receptor – angiotensin-converting enzyme 2 (ACE2) which is abundantly expressed in lungs and kidneys, and excreted into the plasma. The RNA viral genome is complexed with the nucleocapsid (N) protein to form a helical capsid in the virion. Besides, the virion contains the membrane (M), envelope (E), and spike (S) proteins [3]. The M protein has a small ectodomain at its N-terminus and a cytoplasmic tail, while the E protein is hydrophobic. Peplomers of the S protein are present on the surface of the virus, a type I glycoprotein [3]. Additional open reading frames (ORFs) encoded by the virus encode accessory proteins with various functions in viral pathogenesis [4]. Figure 1 illustrates the structure of the causative pathogen.

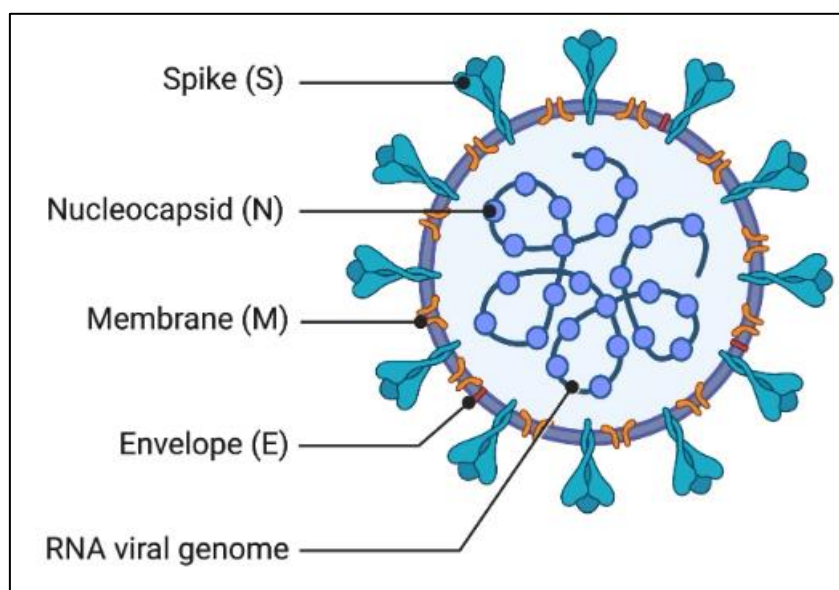


Figure 1. The structure of SARS-CoV-2

2. Innate immune system and SARS-CoV-2

Innate immune responses and related cell populations are essential in the development of clinical signs and severity of COVID-19. The innate immune system is the host's first-line defense against SARS-CoV-2 and other infectious pathogens. Detecting and eliminating infected cells with the assistance of innate immune mechanisms also coordinate and enhance the performance of adaptive immunity. Additionally, innate immunity controls the entrance, translation, replication as well as assembly of viruses. In response to pathogen-associated molecular patterns (PAMPs), cell envelope, endonuclear, and cytosolic pattern recognition receptors (PRRs) trigger inflammatory reactions and programmed cell death, all of which help to limit viral infection and promote clearance [5]. Innate immune cells like DCs, neutrophils, macrophages, and monocytes and innate lymphoid cells (ILCs) like natural killer (NK) cells have abundant PRRs which sense PAMPs or damage-associated molecular patterns (DAMPs) to trigger distinctive immune responses and corresponding inflammatory signaling pathways [3].

Several PRR families, in particular, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), a retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and Toll-like receptors (TLRs) react to SARS-CoV-2 via different signaling pathways [3][5]. These receptors trigger diverse cells, producing interferons (IFNs) to activate specific NK cells, DCs or macrophages to eliminate the virus-infected cells.

2.1. NLRP3 inflammasome sensors in COVID-19

Type I IFNs and inflammatory cytokines are recruited by NLRs. Both PAMPs and DAMPs activate the inflammasome sensor NLRP3, which is one of the most well-researched inflammasome sensors. As a result, the prototypical caspase-1 is activated and gasdermin D (GSDMD) is cleaved [6]. Nlrp3 triggers pyroptosis via forming pores in the plasma membrane of target cells [7].

Typically, macrophages are particularly affected by some SARS-CoV-2 PAMPs. For instance, GU-rich viral RNA from the virus genome activates the NLRP3 and causes macrophages to produce sequent cytokines [8]. *Nlrp3* and *Il1b* mRNA expression in macrophages is upregulated as a result of the E protein of SARS-CoV-2 inducing TLR2 signaling [9]. Additionally, in macrophages taken from COVID-19 patients, the S protein induces the release of interleukin (IL)-1 and upregulates the expression of the NLRP3 protein [10].

2.2. RLRs and IFN signaling in COVID-19

Most ORFs in the SARS-CoV-2 RNA genome are translated via RNA intermediates – subgenomic RNAs. Intracellular RLRs like melanoma differentiation-associated protein 5 (MDA5) and RIG-I can detect and sense such replicative intermediates [3][11]. MDA5 and RIG-I are the RLRs that have received the most attention from researchers, both of which play important roles in how IFN pathways perform [12]. RIG-I and MDA5 move to the target cell's inner membrane of the mitochondria after going through post-translational modifications and getting activated. Then, they interact with mitochondrial antiviral-signaling (MAVS) protein to assemble the MAVS signalosome [13]. Such signalosome activates tumor necrosis factor (TNF) receptor-associated factor (TRAF) 3 and I κ B kinase (IKK) that contribute to the phosphorylation of IFN regulatory factors (IRFs) 3 [13][14]. Such phosphorylation promotes the nuclear translocation and transcription of genes encoding type I IFNs (α and β) and type III IFNs (λ) [3][13]. These IFNs initiate subsequent signaling pathways via different IFN receptors (IFNAR1 and IFNAR2 for IFN- α and IFN- β , IL10R and IFNLR1 for IFN- λ) through a paracrine and autocrine manner to yield numerous IFN-stimulated genes (ISGs) to carry out various antiviral performance [15][16].

2.3. TLRs in COVID-19

Though TLRs are widely distributed in the human respiratory tract, their expression differs amongst distinctive subsets of innate immune cells. For instance, TLR4 is more abundant in

macrophages, whereas TLR3 is prevalent in NK cells [17]. Typically, TLRs utilize two significant adaptor molecules to transduce signals - myeloid differentiation primary response 88 (MyD88) and TIR domain-containing adaptor-inducing IFN- β TRIF [3]. Most TLRs produce inflammatory cytokines via response 88, but TLR3 is a particular case as it only functions via TRIF. TLR4 can bind to and transduce signals via TRIF28 or MyD88 [15]. Nuclear factor (NF)- κ B, mitogen-activated protein kinases (MAPKs), and IRFs are all activated downstream of MyD88, all of which can translocate into nucleus [18]. Such translocation has crosstalk with other PRR families, for it can initiate the generation of ISGs and IFNs as well as the transcription of genes that encode other innate immune sensors like NLRP3. Meanwhile, it triggers the transcriptional initiation of some proinflammatory cytokines like IL-6 and TNF [3][17].

3. Adaptive immune system and SARS-CoV-2

After being invaded by causative pathogens, human body produces CD4⁺ T lymphocytes, cytotoxic CD8⁺ T lymphocytes, and B lymphocytes (antibodies), all of which involve in the regulation of viral infections. However, the functions and significance of each part of adaptive immunity shift with each distinct virus. To combat some viruses and ensure the host's survival, one of the three types of adaptive immunity is essential. When it comes to other types of viral infections, the various forms of adaptive immunity work together rather well and even complement one another, leading to a greater number of potential avenues for effective infection management and sturdy immunity. [19].

After the antigen-presenting cells (APCs) like macrophages or DCs have engulfed the invaded SARS-CoV-2, they reach the lymph node and present the pathogenic antigen to activate different T lymphocytes, especially CD4⁺ T lymphocytes and cytotoxic CD8⁺ T lymphocytes. Cytotoxic T cells are able to directly kill the infected cells while activated CD4⁺ T cells secrete cytokines to aid the proliferation and differentiation of B lymphocytes into plasma cells, and the antibodies secreted by B lymphocytes promote the phagocytosis of pathogens such as macrophages and DCs in the innate immune system.

2.4. CD4⁺ T lymphocytes and COVID-19

T lymphocyte responses are seen in almost every case of COVID-19. Principal control of coronavirus has been linked to the responses of CD4⁺ T lymphocytes, which are more prevalent than those of cytotoxic T lymphocytes [20].

Differentiated CD4⁺ T cells have many functions, including facilitating B lymphocytes, assisting cytotoxic T lymphocytes, recruiting innate immune populations as well as repairing damaged tissues [19]. Typically, when CD4⁺ T cells recognize a virus, they undergo a process of terminal differentiation that results in the development of type 1 T helper (Th1) cells and T follicular helper cells (Tfh). Th1 have antiviral characteristics due to their yield of IFN and related cytokines. The majority of neutralizing antibodies, memory B cells, and long-term humoral immune system are dependent on Tfh [21]. Acute coronavirus infection leads to the development of circulating Tfh cells (cTfh) and cTfh memory cells specific to SARS-CoV-2 [20][23]. The frequency of specific cTfh have been linked to milder cases of the disease [22].

Both CD8⁺ T cell and antibody responses benefit from CD4⁺ T cells. IL-21 is a common cytokine of Tfh and is important for CD4⁺ T lymphocytes to facilitate cytotoxic T lymphocytes [24].

2.5. CD8⁺ T lymphocytes and COVID-19

Cytotoxic T cells are significant in treating viral illnesses as they can directly kill and eliminate virus-infected cells. Better treatment outcomes in COVID-19 cases are related to a larger number of CD8⁺ T lymphocytes specific to SARS-CoV-2 [25].

When a cytotoxic T cell recognize its antigen (coronavirus) and becomes activated, it secretes cytokines, mainly IFN- γ , which has anti-viral microbial properties. Moreover, CD8⁺ T lymphocytes are capable of producing and releasing cytotoxic granules. NK cells also contain these granules,

which include two major protein families: perforin and granzymes. Perforin generates a pore in the plasma membrane of infected cells, enabling granzymes to penetrate their targets. Granzymes are a kind of serine protease that cleaves proteins inside the cell, therefore inhibiting the generation of viral proteins and finally leading to the apoptosis of the infected cells. High levels of IFN, granzyme B and perforin, all of which are associated with powerful cytotoxic effector performance, are present in cytotoxic T cells specific to SARS-CoV-2 in severe case [20][22]. The cytotoxic granules are specifically discharged in the moving direction of infected cells together with the immunological synapse to prevent non-specific collateral harm to normal tissue around the target cells. Cytotoxic T cells can perform serial killing processes as they generate and release the granules, eliminate the target cells, and then shift to the new targets and eliminate again and again.

2.6. B lymphocytes, antibodies, and COVID-19

After the invasion of SARS-CoV-2, naïve B lymphocytes are activated with the assistance of Tfh. CD4⁺ T cells and antigen in the germinal center (GC) induce naïve B cells to proliferate, undergo structural changes via class-switch recombination (CSR) and differentiate, becoming pre-germinal center memory B cells (pre-GC MBCs) and short-lived plasma cells (SLPCs) [26]. These are the low-affinity preliminary antibodies in the early stage. Some of these cells enter the GC to undergo CSR, becoming memory B cells (MBCs) and long-lived plasma cells (LLPCs) and resulting in enhanced antibody affinity via clonal expansion and somatic hypermutation (SHM) [27]. Quick differentiation into plasma cells or generation of a second GC by pre-GC or post-GC MBCs allows for the rapid production of high-affinity antibodies in response to a subsequent invasion or vaccination [28]. These B cells and antibodies travel throughout the body, protecting the central nervous system and the mucosa from further viral infection.

One study measured antibody responses in serum and saliva, reporting that both showed a similar IgG response that lasted for months, while IgA and IgM titers dropped precipitously [29]. Responses in the blood and the mucosa to an antigen are positively correlated with IgG and IgM, while the relationship with IgA is less [29] [30]. High levels of IgG were found in nasal samples from people with severe symptoms, whereas high levels of IgA were found in nasal samples from people with mild to moderate COVID-19.

4. Conclusion

To conclude, both innate and adaptive immunities, are pivotal in fighting SARS-CoV-2. Innate immune cells have abundant PRRs, including NLRs, RLRs, and TLRs, which respond to PAMPs to sense and kill infected cells rapidly. After the APCs like macrophages or DCs present the antigen and reach the lymph node, different T lymphocytes, especially CD4⁺ T lymphocytes, cytotoxic T lymphocytes and B lymphocytes, are activated to build up long-term protection in defense of COVID-19.

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