IMMUNE RESPONSE AGAINST SARS-COV-2

Resposta Imune Contra O SARS-CoV-2

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Abstract

Coronaviruses (CoVs) are a large subfamily of enveloped, single positive-strand RNA viruses. The first case of SARS-CoV-2 infection was identified in December 2019, after sequencing clinical samples from a cluster of patients with unknown origin pneumonia cases in Wuhan, China. Patients may be asymptomatic or experience mild, moderate or severe symptoms, with or without pneumonia. The severe patients generally require hospitalization on intensive care centers, and will eventually need mechanical invasive ventilation. In this review we approach the latest understanding of literature about the immune response mechanisms against the intracellular pathogen SARS-Cov-2, and review the aspects of innate and adaptive immune responses, and possible evasive mechanisms of these responses by the virus. The understanding of these mechanisms is crucial for the development of therapeutic and immune preventive strategies against the COVID-19, which has configured an important pandemic with high rates of mortality.

Keywords: SARS-CoV-2; COVID-19; Innate Immune response; Adaptive Immune response; Pathogenesis.

Resumo

Os coronavírus (CoVs) são uma grande subfamília de vírus de RNA de fita positiva simples e envelopados. O primeiro caso de infecção por SARS-CoV-2 foi identificado em dezembro de 2019, após o sequenciamento de amostras clínicas de um grupo de pacientes com casos de pneumonia de origem desconhecida em Wuhan, China. Os pacientes podem ser assintomáticos ou apresentar sintomas leves, moderados ou graves, com ou sem pneumonia. Os pacientes graves geralmente requerem internação em leitos de terapia intensiva pela necessidade de ventilação mecânica invasiva. Nesta revisão, abordamos a mais nova compreensão da literatura sobre os mecanismos de resposta imune contra o patógeno intracelular SARS-Cov-2, contemplando desde aspectos das respostas imunes inata e adaptativa, e possíveis mecanismos de evasão da resposta imune por estes vírus. A compreensão destes mecanismos é fundamental para o desenvolvimento de estratégias terapêuticas e imunoprofiláticas contra a COVID-19 que tem configurado uma preocupante pandemia com altas taxas de mortalidade.

Palavras-chave: SARS-CoV-2; COVID-19; Resposta Imunológica Inata; Resposta Imunológica adaptativa; Patogênese.

1. INTRODUCTION

Coronaviruses (CoVs) are a large subfamily of enveloped, single positive-strand RNA viruses belonging to the *Coronaviridae* family, which can infect humans and several other animals (Azkur et al., 2020; Coronaviridae Study Group of the International Committee on Taxonomy of, 2020). There are three coronaviruses that can infect humans: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the Novel Coronavirus (SARS- CoV-2). It has been hypothesized that this β-CoVs are originated from bats and transmitted to humans via cats or camels in SARS-CoV and MERS-CoV, respectively (J. Cui, Li, & Shi, 2019). Through a phylogenetic comparison of SARS-CoV-2 with other CoVs, bat coronavirus (BatCoV-RaTG13) showed higher genome similarity, about 96%, favoring the hypothesis that the novel coronavirus are also originated from bats (N. Dong et al., 2020; Y. Zhou et al., 2020), and among human coronaviruses, SARS-CoV showed the higher genetic similarity, about 79% (Coronaviridae Study Group of the International Committee on Taxonomy of, 2020).

The first case of SARS-CoV-2 infection was identified in December 2019, after sequencing clinical samples from a cluster of patients with unknown origin pneumonia cases in Wuhan, China (N. Zhu et al., 2020). The disease caused by SARS-CoV-2 infection, named Coronavirus Disease-2019 (COVID-19), have many different clinical presentations and high similarity with many other viral respiratory infection symptoms. Patients may be asymptomatic or experience mild, moderate or severe symptoms, with or without pneumonia (X. Dong et al., 2020; Guan et al., 2020). The asymptomatic patients are fully capable of transmitting the virus, making this disease easily spreading all over the world (Bai et al., 2020; Rothe et al., 2020). Approximately 20% of patients presents with severe disease and require hospitalization, and 5% require Intensive Care Units (ICU) (Azkur et al., 2020). These patients generally require mechanical ventilation and tend to remain ventilator dependent for 10–14 days, and most of them presents poor prognosis (Bhatraju et al., 2020; Vardhana & Wolchok, 2020; C. Wu et al., 2020).

The fast natural spread of this virus; longer median incubation time, that create a large window of time for transmission; high proportion of severe cases with higher rates of mortality and some immune response particularities (considered an aggravating factor), turns immunity unable to control this microorganism efficiently and has been explored to explain the global devastation by SARS-CoV-2 infection (Guan et al., 2020; Q. Huang et al., 2020; Vardhana & Wolchok, 2020).

Thus, on 30 January 2020, the World Health Organization (WHO), declared the outbreak of SARS-CoV-2 infection a Public Health Emergency of International Concern (PHEIC) and provides

social isolation recommendations to minimize the rates of viral transmission and avoid a possible general collapse of health care centers around the world (WHO, 2020). This situation had increasing the number of publications rapidly to support the action planning of health authorities and professionals. The knowledge of the immune response to this infection is still being studied by several groups, but some mechanisms involved in the protection and in the pathogenesis of the disease has been described.

To a better understanding the immune response on COVID-19, in this review, we aimed to summarize the newly knowledges about the immune response mechanisms involved on SARS-CoV-2 infection, and the possible evasive mechanisms of the virus to these responses.

2. INNATE IMMUNE RESPONSE

SARS- CoV-2 is transmitted primarily via respiratory droplets with viral particles when an infected person coughs or sneezes. Even though uncommon, fecal-oral transmission route has been also reported. The median incubation period is about 4-5 days before symptom onset, and 97.5% of symptomatic patients developing symptoms within approximately 11 days (Guan et al., 2020; Lauer et al., 2020; Q. Li et al., 2020; Pung et al., 2020; Tay, Poh, Renia, MacAry, & Ng, 2020). The clinical features typically observed in COVID-19 patients are common to other diseases with respiratory symptoms, such as fever, sore throat and dry cough. Other unspecific symptoms, most unusual, like muscle and/or joint pain, headache/dizziness, diarrhea, nausea, were also reported (G. Li et al., 2020). Around 80% of patients with a mild to moderate presentation and self-limiting course has a classical respiratory virus-like clinical course (Azkur et al., 2020; C. Huang et al., 2020). Although the benign course in most of the infected patients, which needs only basic cares and social isolation at home, other patients can present a severe form with an extensive lung commitment, manifested by a stronger difficulty in breathing, until coughing with blood and needs of urgent hospitalization.

Dysregulation on immune system with a high increase of neutrophils, lymphopenia, with a decrease of CD4+ T cells, have been associated to severe cases of COVID 19. This causes a systemic inflammation and can be a potential critical condition in the tissue damage on various organs (Azkur et al., 2020). Elevated serum cytokines and chemokine levels (called “cytokines storm”) were correlated with the severity of the disease and adverse outcomes (Chan et al., 2020; G. Chen et al., 2020; N. Chen et al., 2020; C. Huang et al., 2020; Liu et al., 2020; Phan et al., 2020).

The immune system governs the resolution of the infectious diseases. In general, the first step in a viral infection is virus binding to a host cell through its target receptor. The host innate immune

system detects viral infections by using Pattern Recognition Receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs). PAMPs include lipids, lipoproteins, proteins, and nucleic acids of the bacterial, viral, parasite, and fungal origins (Kawai & Akira, 2010). The PRRs mainly known include toll-like receptors (TLR), RIG-I-like receptor (RLR), NOD-like receptor (NLR), C-type lectin-like receptors (CLRs), and some free-molecule receptors in the cytoplasm, such as cGAS, IFI16, STING and DAI (G. Li et al., 2020). RIG-I-like receptors (RLRs), including the H family members RIG-I (DDX58), MDA5 (IFIH), and LGP2, primarily recognize nucleic acids of RNA viruses (Kell & Gale, 2015; Yoneyama & Fujita, 2009).

When a virus invades the host, PRRs initially recognize the viral nucleic acid, bind to the specific signal adapter protein, at a molecular level, activating IRF3 and IRF7 signalling pathway, before being translocated to the nucleus and promote the synthesis of type I interferons (IFNs). Type I IFNs subsequently activate the downstream JAK-STAT signal pathway, promote the expression of IFN-stimulated genes (ISGs) (Nelemans & Kikkert, 2019). The type I interferons response induces several mechanisms to protect all cell of the body against viral entry, blocking the expression of virus receptor in the cell membranes, reduces viral replication in infected cells, and activate an inflammatory response that improves innate response killing mechanisms against the virus, besides improving antigen presentation and recognition of the virus by adaptive immune response (Abbas, Lichtman, & Pillai, 2017; Azkur et al., 2020).

Moreover, a type of innate immune lymphoid cells, the Natural Killer (NK) cells, are important to recognize and kill viral infected cells via their spontaneous cytolytic activity and secreting a variety of soluble mediators (Ahmad et al., 2001; Husain et al., 2002). NK cells association along with Cytotoxic lymphocytes (CTLs) are necessary for the control of viral infection (Zhang et al., 2019). However, an inhibitory receptor, called NKG2A, has been demonstrated to induce NK cell and CD8+ T cells exhaustion in chronic viral infections (F. Li et al., 2013) and this functional exhaustion has been reported to have a positive correlation with disease progression (Andre et al., 2018).

In SARS-CoV infection, an earlier research demonstrated that this virus has a tropism to airway epithelial cells, alveolar epithelial cells, vascular endothelial cells and macrophages in the lung, all of which express the angiotensin-converting enzyme 2 receptor (ACE2) (Hamming et al., 2004; Jia et al., 2005; H. Xu et al., 2020). SARS-CoV-2 uses the same entry receptor, a promising host target receptor that is been used to infect cells, and the same cell subsets are likely targeted by this virus (Walls et al., 2020; P. Zhou et al., 2020).

Studies on SARS-CoV shows that multiple viral structural and non-structural proteins antagonize interferon responses. Antagonism occurs at various stages of the interferon signaling pathway, including by preventing PRR recognition of viral RNA (Siu, Chan, Kok, Chiu-Yat Woo, & Jin, 2014; Sun et al., 2012; Versteeg, Bredenbeek, van den Worm, & Spaan, 2007), by preventing PRR signaling through TBK1/inhibitor of nuclear factor-κB kinase subunit-ε (IKKε), TRAF3 and IRF3 (Frieman, Ratia, Johnston, Mesecar, & Baric, 2009; Siu et al., 2014), by preventing downstream interferon signaling through STAT1 (Frieman et al., 2007) and by promoting host mRNA degradation and inhibiting host protein translation (Narayanan et al., 2008). The mechanism involved is still unknown, could be the same as SARS-COV, but, in fact, it has been demonstrated that SARS-CoV-2 did not significantly induce types I, II, or III interferons in the infected human lung tissues, and present a more efficient virus replication (Chu et al., 2020).

Inside the cells, SARS-CoV-2 promotes a local immune response by increased recruiting macrophages and monocytes, which are the first cell lines against viral proliferation. In most cases, this process can resolve the infection. However, in other cases, a dysfunctional immune response occurs promoting an extensive inflammation process, which can cause severe destruction of lung cells and even systemic pathology (Tay et al., 2020). Furthermore, the total number of NK was decreased markedly in patients with SARS-CoV-2 infection and the function of this cells was exhausted along with an increased expression of NKG2A, significantly higher in COVID-19 patients, as compared to healthy controls (M. Zheng et al., 2020).

In addition, patients infected with SARSCoV-2 presents lower percentages of cells with CD107a+ NK, IFN-γ+ NK, IL-2+ NK, and TNF-α+ NK cells and the mean fluorescence intensity (MFI) of granzyme B+ NK cells are also reduced than in healthy controls. Consistent with these findings, a decreasing percentage of CD107a+ CD8+, IFN-γ+CD8+, and IL-2+CD8+ T cells and MFI of granzyme B+CD8+ T cells were also observed in COVID-19 patients. Taken together, these results confirmed the functional exhaustion of cytotoxic lymphocytes and NK cells in COVID-19 patients. (M. Zheng et al., 2020).

Importantly, in patients convalescing after therapy, the number of NK and CD8+ T cells was restored along with a reduction of NKG2A expression. These results suggest that the functional exhaustion of NK cells and cytotoxic lymphocytes might be associated with SARS-CoV-2 infection to produce a break down in the early stages of antiviral immunity (M. Zheng et al., 2020).

Another pathway from the immune response that is associated to the pathogenesis of the COVID 19 is the IL-1β's pathway. This cytokine is released during pyroptosis, a highly inflammatory

form of programmed cell death that is commonly associated with cytopathic viruses and can trigger a subsequent inflammatory response. In antagonism of the interferon response, pyroptosis aids viral replication, resulting in increased release of products that can further induce aberrant inflammatory responses. IL-1 β is elevated during SARS-CoV-2 infection (C. Huang et al., 2020), and some of these pathways are described in SARS- CoV-2 (Tay et al., 2020). In this way, the sudden and intense increase of IL-1β production can antagonize the effects of type I interferons, suppressing antiviral responses and resulting in cytokine storm (Mayer-Barber & Yan, 2017).

Furthermore, the cytokine storm has been reported to be a mediator of this widespread lung inflammation. In comparison with mild cases, patients with severe COVID-19 showed a significantly higher percentage of CD14+CD16+ inflammatory monocytes in peripheral blood (Y. Zhou et al., 2020). These cells secrete inflammatory cytokines that contribute to the cytokine storm, including MCP-1, IP-10 and MIP1α (Tay et al., 2020). So, as observed in blood plasma samples, higher levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), IP-10, MCP-1, macrophage inflammatory protein 1α (MIP-1α) and tumor necrosis factor (TNF) were reported in severe cases of COVID-19 (C. Huang et al., 2020). Noteworthy, IL-6 levels in these patients continue to increase over time and are relatively more elevated in non-survivors than in survivor patients (F. Zhou et al., 2020).

3. ADAPTATIVE HUMORAL RESPONSE

The adaptive humoral response develops after the virus antigens are recognized by B cells, get activated and functioning as an antigen-presenting cell (APC), presents part of the virus antigens to CD4+ T cells, that gives the signaling to B cells to produce antibodies. These mechanisms take around 72 hours to be fully developed and produce antibodies that are effective against the virus (Abbas et al., 2017). In general, B lymphocytes, under a stimulus of antigens, undergo differentiation into plasma cells and produce different classes of immunoglobulin/antibodies or can continue in circulation as antigen sensitive memory cells. In virus clearance, neutralizing antibodies (NAbs) have been considered as a key immune product for protection or treatment against viral diseases (F. Wu et al., 2020). The IgM isotype primary virus-specific antibody response is observed within the first week following symptoms and IgG, isotype antibodies follow the early IgM response that mostly retain a life-long immunity (Long et al., 2020). The life-long immunity is crucial to have a faster response in a sequential exposure to the virus and is associated with the presence of a long-lasting memory T and B cells in lymph nodes.

Virus-specific antibodies were detectable in 80–100% of patients at 2 weeks after symptom onset on SARS and MERS (Corman et al., 2016; Hsueh, Huang, Chen, Kao, & Yang, 2004; G. Li, Chen, & Xu, 2003; Long et al., 2020). For SARS-CoV-2 infection, viral peak is commonly earlier in comparison to SARS-CoV patients, so approximately 1 week after symptoms onset, B cell responses can be observed concomitantly with T follicular helper cell responses in patients with COVID-19 (J. Y. Kim et al., 2020; Pan, Zhang, Yang, Poon, & Wang, 2020; Zou et al., 2020). However, as most of world population has not have previous contact with this virus, there are probable not a memory response for this virus, and this might delay a protective humoral response to occur.

In the course of COVID-19, similar to others viral diseases, in the acute phase, an increase in virus-specific IgM can be observed, followed by an increase in virus-specific IgG at later phases (Azkur et al., 2020; X. Dong et al., 2020). In spite of antibody responses also arise earlier in SARS-CoV-2 response, some patients may not develop long lasting antibodies (IgG) (Tay et al., 2020).

A Receptor Binding Domain (RBD) is the primary target of neutralizing antibodies (Z. Zhu et al., 2007), which can independently bind to the host target ACE2 receptor and turns the immune system capable of target neutralizing epitopes effectively (Qiu et al., 2005; Tay et al., 2020; S. K. Wong, Li, Moore, Choe, & Farzan, 2004; Xiao, Chakraborti, Dimitrov, Gramatikoff, & Dimitrov, 2003). Despite neutralization of the virus be an important mechanism of action for antibodies, the specific titer and specificity of the antibody repertoire required (for protection) remains unclear.

Other function of antibodies includes, opsonization of virus into phagocyte cells, complement activation and antibody-dependent cellular cytotoxicity (ADCC), in which the antibodies bound to the virus or cells expressing virus antigens, bind to NK cells and activate this cell to kill the infected cells.

Apparently, SARS-CoV does not have strong mechanisms to escape or prevent antibody neutralization and most patients develop neutralizing antibodies by 3 weeks after infection (Berry et al., 2010; Nie et al., 2004; Temperton et al., 2005). Thus, if SARS- CoV-2 behaves like other SARS-CoV in this respect, it is supposed that efforts in developing neutralizing monoclonal antibodies to treat COVID-19 patients might be successful (Tay et al., 2020). In support to that, studies have reported 10 severe patients that received convalescent serum therapy, and demonstrated improved lung function, oxygenation, reduced inflammation, and viral load (Azkur et al., 2020; Cunningham, Goh, & Koh, 2020). Therefore, infusion of the convalescent serum therapy obtained from already recovered patients can be tested to prevent or limit SARS-CoV-2 infection.

Secretory influenza hemagglutinin (HA)-specific IgA response in the respiratory tract is more effective and more cross protective against influenza infections than the systemic immunity induced by parenteral vaccines in human and mice models (Liew, Russell, Appleyard, Brand, & Beale, 1984; Tamura et al., 1990). In the context of SARS-CoV infections, mucosal immunity via IgA may be important for preventing infection. In influenza infection, for instance, IgA plays a crucial role in the protection on mucosal surfaces by neutralizing the virus or preventing the attachment of viruses to the mucosal epithelium (Azkur et al., 2020). SARS-CoV-specific IgA may play a role in protection for the vaccinated mice with SARS (See et al., 2006). Intranasal vaccination with recombinant adenovirus that have SARS genome induced local IgA and systemic IgG neutralizing antibodies and specific T-cell responses, which are able to protect against SARS-CoV infection in animal models (Azkur et al., 2020; B. J. Zheng et al., 2008). However, although passive immunization was sufficient to prevent infection of the lung in influenza, it did not protect the upper respiratory tract of mice and ferrets against viral infection (Renegar, Small, Boykins, & Wright, 2004). In MERS-CoV-S1, specific neutralizing IgA antibodies in the bronchoalveolar lavage fluid were shown to be protective in mice (M. H. Kim, Kim, & Chang, 2019). Studies on humoral immune response to SARS-CoV-2 showed an early IgA response, instead of IgM, in COVID-19 patients, and IgA response appears and grows early, peaks at week 3, and it is stronger and more persistent than the IgM response (Padoan et al., 2020; Yu et al., 2020).

4. ADAPTATIVE CELLULAR RESPONSE

After recognize viral particles the antigen-presenting cells (APC - mainly dendritic cells and macrophages) presents viral peptides to CD4+ T cells through MHC-Class-II molecules (Azkur et al., 2020; Jansen, Gerlach, Elbahesh, Rimmelzwaan, & Saletti, 2019). Dendritic cells (DCs) are professional antigen-presenting cells linking innate and adaptive immunity and play an important role in several infectious diseases, especially in viral responses. The respiratory tract has some immature DCs which promotes immune surveillance and respond dynamically to local tissue inflammation. Macrophages phagocyte microbes, process and present their antigens to CD4+ T cells in MHC-class-II. These cells express a wide range of c-type lectin receptors and Toll-like receptors for recognition of conserved pathogen patterns and induction of subsequent immune responses (Lau, Peiris, & Law, 2012).

After being activated by APC, T helper cells produce pro inflammatory cytokines via the NF-κB signaling pathway maintaining the stimulus of immune cells to local response (Manni, Robinson,

& Alcorn, 2014). For instance, IL-17 cytokine recruit monocytes and neutrophils to the site of infection with inflammation and activate other downstream cytokine and chemokine cascades, such as IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1 (Bunte & Beikler, 2019). IFN-γ activate macrophages to produce Reactive oxygen species (ROS) and both IFN-γ and IL-4 activate B cells to produce highly specific antibody response comprised by somatically mutated higher affinity class-switched antibodies (Abbas et al., 2017).

Infected DCs by SARS-CoV showed a lack of antiviral cytokine response, intense chemokine up-regulation, induction of CCR expression and strong expression of TRAIL. This findings suggest possible evasive mechanisms of immune response, and amplification of immunopathology in infections by SARS-CoV virus (Frieman, Heise, & Baric, 2008). Altered APC function and impaired DC migration resulting in reduced priming of T cells likely contribute to fewer number of virus-specific T cells in the lungs (Channappanavar, Zhao, & Perlman, 2014; Yoshikawa, Hill, Li, Peters, & Tseng, 2009; Zhao, Zhao, Van Rooijen, & Perlman, 2009).

Another cell involved in protective response against virus infection is CD8+ T cells. The classical mechanism is that T cell receptor of the CD8 cytotoxic T cells recognizes the viral peptides presented by MHC-class-I molecules of virus infected cells and are cytotoxic to virus infected cells via multiple mechanisms including perforin and granzymes (Retamal-Diaz et al., 2019). CD8 T cells are critical for mediating clearance in many acute viral infections in the lung. After became activated, these cells start dividing and show clonal expansion and develop virus-specific effector and memory T cells and lyse the virus-infected cells in the tissues (Azkur et al., 2020).

In addition, T regutatory cells (Treg) have an important role during an infection, by suppressing excessive immune responses to pathogens, growing of cancer cells, response against transplanted organs and to prevent and control the development of autoimmune and allergic diseases (Akdis & Akdis, 2009; Palomares, Akdis, Martin-Fontecha, & Akdis, 2017). In respiratory virus infections, Treg cells can limit the effector cells responses and reduce the tissue damage on airway mucosa and pulmonary immunopathology (Lan, Zhang, Bachert, & Zhang, 2020; Loebbermann, Durant, Thornton, Johansson, & Openshaw, 2013; Suvas, Azkur, Kim, Kumaraguru, & Rouse, 2004).

The acute phase of SARS in human patients was associated with marked leukopenia with severe lymphopenia (*80% of patients), involving a dramatic loss of CD4+ T cells (*90–100% of patients) and CD8+ T cells (*80–90% patients) in comparison with healthy control individuals

(Channappanavar et al., 2014; W. Cui et al., 2003; T. Li et al., 2004; R. S. Wong et al., 2003). Moreover, the absolute numbers of CD4+ T cells, CD8+ T cells, and B cells were gradually decreased with severity of illness on COVID-19. Moreover, it is observed an increase of activation markers on CD4+ and CD8+ T cells and a decrease of the percentage of Treg cells in severe and extremely severe patients (Wang et al., 2020).

Nonetheless, the data on number and function of T cells are inconsistent in COVID-19 patients, as a loss of natural Tregs is observed, along with increased IL-10 levels in these patients, there is a hypothesis that hyperfunction of remaining CD4+ and CD8+ T cells is associated with the pathogenesis of extremely severe SARS-CoV-2 infection (Wang et al., 2020). In addition, CD8+ T cells count were for about 80% of total infiltrative inflammatory cells in the pulmonary interstitium of SARS-CoV infected patients and play a vital role in clearing CoVs in infected cells, but also induce immune injury (Maloir, Ghysen, von Frenckell, Louis, & Guiot, 2018).

Interestingly, analyses by flow cytometer showed an increase in the percentage of CD4+ naïve T cells (CD3+CD4+CD45RA+) and a decrease in memory helper T cells (CD3+CD4+CD45RO+) in peripheral blood on severe cases of COVID-19, when compare to non-severe cases. The percentage of CD3+CD8+CD28+ cytotoxic T cells also decreased. However, there was no significant difference in activated total T cells (CD3+HLADR+) and activated cytotoxic T cells (CD3+CD8+HLA-DR+). These severe patients also presented with lower levels of regulatory T (Treg) cells (CD3+CD4+CD25+CD127low+) (Qin et al., 2020). In addition, the overactivation of T cells, manifested by an increase in T-helper (Th)17 and the high cytotoxicity of CD8+ T cells, partially accounts for the severe immune injury observed in these disease (Z. Xu et al., 2020).

5. CONCLUSIONS

This review has presented the most recent knowledge of the literature about the innate and adaptive immune responses mechanisms against the intracellular pathogen SARS-Cov-2. Although many mechanisms of protection and pathogenesis still needs to be clarified, fast evolving knowledge of this disease has been achieved, due to a high involvement of the scientific community in resolving this important worldwide problem. Problems affecting the sensors and function in the first innate immune response cells, and B and T cells activation/effector function have been detected in the disease. A role of virus cytopathic effect, and the inflammation mediated by the immune response may play a role in the pathogenesis of the disease. The understanding of immunological relevant mechanisms to combat SARS-Cov-2 infection and modulate immunopathology can serve as bases to building of new immunological concepts and clinical therapies for COVID-19.

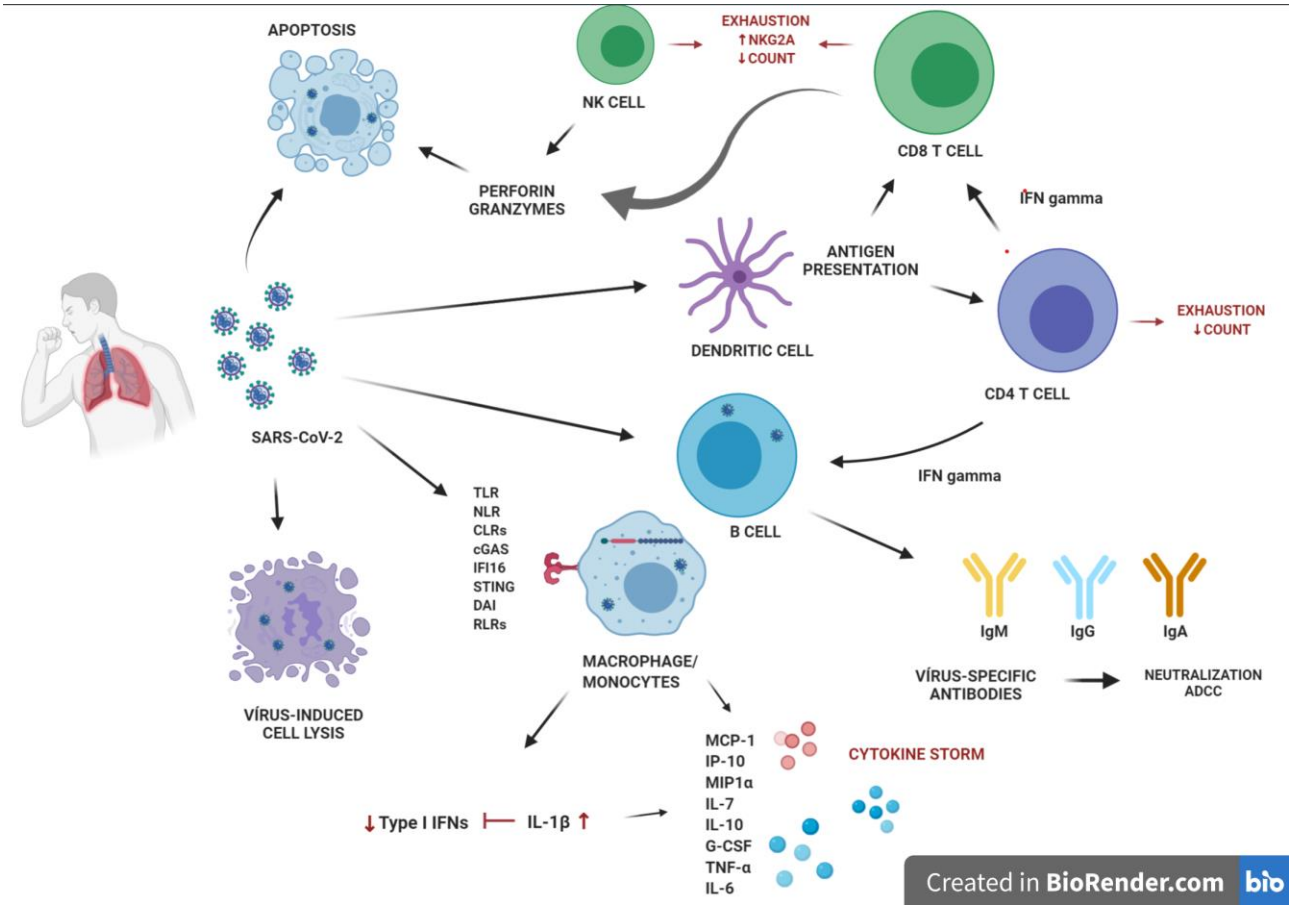

Figure 1. Proposed mechanisms of immune response to SARS-CoV 2 and evasive mechanisms of the virus, based on the recent literature data of the immune response observed in COVID 19 patients.

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