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Immune response in acute respiratory syndrome induced by the new coronavirus

Waldemar de Paula Júnior[1,2], Carina Silva de Freitas[1], Francisco Ferreira de Lima Neto[1], Nathália Alves Santana[1], Nathália Zenaide Durães Soares[1], Vitória Louise Mendes Fonseca[1], Renata Cristina Rezende Macedo do Nascimento[2], Andrea Grabe-Guimarães[2]

[1]Departamento de Fisiopatologia, Universidade Estadual de Montes Claros (UNIMONTES) - Montes Claros (MG), Brazil
[2]Escola de Farmácia, Universidade Federal de Ouro Preto (UFOP) - Ouro Preto (MG), Brazil

Corresponding author: Waldemar de Paula Júnior - Departamento de Fisiopatologia - Universidade Estadual de Montes Claros – Campus Universitário Prof. Darcy Ribeiro - Avenida Rui Braga, s/n - Vila Mauricéia – CEP: 39401-089 - Montes Claros (MG), Brazil E-mail: waldemar.junior@unimontes.br

ABSTRACT

Coronaviruses (CoVs) belong to the family *Coronaviridae*, which are enveloped and have a single-stranded RNA genome. The new coronavirus (SARS-CoV-2) is the seventh known coronavirus that can infect humans and cause serious illness, such as acute respiratory syndrome. The coronaviruses already identified have contributed to the understanding of the clinical manifestations caused by SARS-CoV-2, as well as their associations with the immune system. The aim of the present study was to carry out a narrative review of the literature on the host's immune response to infection by the new coronavirus. The review contains basic and summarized information on the main mechanisms involved in the immune response to SARS-CoV-2. The characteristics of the infection were considered according to the following: from the initial contact with the host through binding to angiotensin-converting enzyme 2 (ACE-2); the recognition of the pathogen by innate immunity cells; its containment mechanisms, including the production of effector cytokines and chemokines important in the development of the inflammatory process; and the participation of the complement system until the activation of the adaptive immune response. The probable occurrence of a host dysfunctional immune response and the escape mechanisms of the virus were also addressed. Despite numerous studies on the pathogenesis of SARS-CoV-2 infection, knowledge about the host's immune response in COVID-19 is not fully understood. The present work established the relationship between the new coronavirus and the immune system, but further studies are needed for all the mechanisms of the process to be elucidated.

Keywords: SARS virus; immunity; COVID-19; Coronavirus infections.

INTRODUCTION

Coronaviruses (CoVs) belong to the family *Coronaviridae*, are enveloped, have a single-stranded, positive-sense RNA (Ribonucleic Acid) genome[1]. The main structural genes of the viruses encode four proteins: the nucleocapsid protein (N), the spike (S), the envelope protein (E), and the membrane glycoprotein (M). Hemagglutinin esterase (HE) is present in some CoVs but is not found on the surface of SARS-CoV-2. The M and E proteins are M important in virus morphogenesis, assembly and budding, while

the S protein, represented by crown-like projections, is responsible for its entry into host cells[1,2].

SARS-CoV-2 (Severe Acute Respiratory Syndrome - Coronavirus 2) is the seventh known coronavirus with the ability to infect humans. The new coronavirus (SARS-CoV-2), SARS-CoV and MERS-CoV (Middle Eastern Respiratory Syndrome - Coronavirus) are all three capable of causing severe illness, including severe acute respiratory syndrome (SRA)[3]. The genomic sequence of SARS-CoV-2 contains similar composition by 79.0% and 51.8% with SARS-CoV and MERS-CoV, respectively[1].

The clinical manifestations caused by SARS-CoV-2 include symptoms of acute respiratory infection, which can rapidly progress to acute respiratory failure and other complications[4].

SARS-CoV-2 is easily transmitted through respiratory secretions, survives in external environments, and, besides causing the signs and symptoms mentioned above, can induce deleterious, inhibitory, and maladjusted immune response mechanisms, effects that have not yet been clarified[4]. Therefore, it is important to discuss its characteristics and the relationship with the host, contributing to new useful evidence in its control and treatment.

The purpose of this study was to describe the relationship of the immune system with the new coronavirus, demonstrating its importance in controlling the infection and its role in the severity of COVID-19. Evaluating the immune response to an infection is important because of its contribution to understanding the behavior of the infectious agent in the human body and the possibility of developing pharmacological and non-pharmacological measures, such as vaccines, for disease control and eradication. For infections caused by new pathogens, this concern becomes even more important and urgent, especially when the infection is contagious, easily spread, and can become severe and lethal as the one caused by SARS-CoV-2.

This is a narrative review that also addresses the defense mechanisms used by the human body against the new coronavirus, highlighting the morphological and functional characteristics of the components of innate and adaptive immunity, their mechanisms of integration, and their participation as an important element in the progression of the disease.

General characteristics of the immune system

Immunity is divided into innate and adaptive responses. The former reacts from the beginning of an infection in a non-specific manner, perpetuating itself throughout the response to the pathogen, while adaptive immunity responds late and specifically, with the generation of immunological memory[5]. Innate immunity is mediated by cells such as monocytes, macrophages, neutrophils, and natural killer (NK) cells, while T and B lymphocytes represent adaptive immunity[6].

Initially, innate immunity is formed by physiological and anatomical barriers, which constitute the first defense contact of the organism. Then, specialized cell response mechanisms are activated, such as phagocytosis, inflammatory process, complement system, and synthesis of proteins, cytokines, and chemokines[7]. The activation of innate immunity mechanisms is based on the recognition of pathogen-associated molecular patterns (PAMPs), by pattern recognition receptors (RRPs) such as Toll-like receptors (TLRs), present mainly in macrophages, neutrophils and dendritic cells (DCs), and also RIG-I (Retinoic Acidinducible Gene I) receptors, NOD-like receptors (NLR), C-type lectin-like receptors, scavenger receptor and N-Formil receptors[8,9]. In addition, the receptors can detect molecules produced by host cells that indicate cell damage. After the recognition step, the standard receptors, including TLRs and RLRs (RIG-I-Like Receptors), activate the transcription factors NF-κB (Nuclear Factor Kappa B) and AP-1 (Activator Protein 1), inducing the production of effector cytokines and pro-inflammatory chemokines and of transcription factors IRF (Interferon Regulatory Factor) that stimulate the production of interferons important in the development of the inflammatory process and antiviral response[10].

Another type of response developed is the activation of the complement system, consisting of approximately thirty proteins, with an important role in innate immunity, whose functions involve opsonization, lysis mediated by the membrane attack complex (MAC), and chemotaxis[11].

The main characteristics of adaptive immunity are specificity and diversity of recognition, memory, response specialization, self-limitation, and tolerance to components of the body itself[12]. Adaptive immunity involves regulated interaction between antigen presenting cells and T and B lymphocytes, which develop and are activated within a series of lymphoid organs, components of the lymphatic system, divided into primary and secondary organs [7]. Primary organs provide microenvironments specialized in generating the primary repertoire of B and T lymphocytes. In contrast, secondary lymphoid tissues are specialized in coordinating immune responses[13].

Based on their phenotypes and functions, T lymphocytes mainly include CD4+ T cells (helper or auxiliary) and CD8+ T cells (cytotoxic or cytolytic). CD4+ T cells can be divided into at least five functional subsets: T helper (Th)1, Th2, Th17 and T helper follicular helper (Tfh) cells, which tend to promote adaptive immune responses, and regulatory T cells (Treg), which generally suppress inflammation. CD8+ T cells are composed of the following subgroups: cytotoxic T cells (Tc), the main effector cells of adaptive immunity, especially in viral infections, and CD8+ Treg cells, which inhibit Th cell activity and suppress immune responses to infection[14].

Several factors related to the host and the infectious agent influence the performance of immune system components. Therefore, there is a need to understand the pathogen-host interaction, especially in the infection caused by SARS-CoV-2, recently discovered and considered a global public health emergency. In this sense, the present work will emphasize the immunological mechanisms related to viral infections, especially immunity against the new coronavirus.

Antiviral immunity

Host antiviral responses are essential for controlling viral replication, limiting the spread of a virus, and destroying infected cells[15]. In viral infections, receptors, especially TLR3, TLR7, TLR8, and TLR9, can detect virus components[16]. TLR7 detects single stranded RNA (ssRNA) oligonucleotides containing guanosine- and uridine-rich sequence. Recognition happens on the endosomes of plasmacytoid DCs and B cells. TLR8 is preferentially expressed in DCs and myeloid monocytes and also recognizes ssRNA[17].

After recognition of a virus by the PAMP-RRP association, TLR signaling regulates the expression and secretion of pro-inflammatory cytokines and co-stimulatory molecules via the NFkB molecule[18]. Type I Interferons (IFN-α and IFN-β) produced mainly by macrophages and dendritic cells, interact with specific receptors located on neighboring cells, stimulating the transcription of genes that act in inhibiting virus replication. In addition, IFNIs activate natural killer cells, which are important in eliminating infected cells. IFNs also regulate the expression of major histocompatibility complex class I (MHC-I) molecules, fundamental in the antigen presentation process. Thus, they induce recognition of infected cells by cytotoxic T lymphocytes, establishing the beginning of the adaptive response[19].

The mechanism of action of TCD8+ cells involve the release of granzymes and perforins and, subsequently, lysis of infected cells18. T helper lymphocytes also participate in viral infections and can stimulate B cells to produce antibodies, important in neutralizing viral particles and activating NK cells[20].

Knowledge about the immune response evident in SARS-CoV-2 infection is still limited, and most of the understanding is based on the immune response to other coronaviruses. The evaluation of more substantiated and specific immune responses will require years of infection in the population. This paper, although not an original article, includes data on virus immunity in the context of SARS-CoV-2 infection and discusses recent findings on the new coronavirus, relating consolidated information with other respiratory viruses of the same family. This review can contribute to a better understanding of the antiviral immune response, the immunity concerning the new coronavirus, and its escape mechanisms. It is written in clear language and scientifically supported and can be used in the academic community and society in general as a quick search for information about the interaction of SARS-CoV-2 with the human organism.

Immunity to SARS-COV-2

SARS-CoV-2 infection and lung injury trigger a local response with recruitment of macrophages and monocytes that release cytokines and initiate T and B cell responses. In most cases, this process can control the infection. However, a dysfunctional immune response may occur, causing severe lung damage and systemic disease[21].

During the initial phase of infection, viruses infiltrate the lung parenchyma, proliferate, and generate mild constitutional symptoms associated with a macrophage response. Collateral tissue injury and the inflammatory processes that follow cause additional lung damage, hypoxemia, and cardiovascular stress. In certain patients, the host inflammatory response continues and amplifies, even with reduced viral load, resulting in systemic inflammation[22]. The pathophysiology of SARS-CoV-2 infection resembles that of SARS-CoV infection, with aggressive inflammatory responses. Therefore, disease severity is related to viral infection and immune response[21].

CoVs infection initiates from the binding of the virus S protein to a host cell (Figure 1). The receptor used by SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), which is present in many cell types, including epithelial cells of the nasal and oral mucosa, and in lung tissue, thus in the upper and lower respiratory system. After binding, fusion occurs between the novel coronavirus and the host cell and release of the viral RNA into the cytoplasm of the cell[23]. The genome of SARS-CoV-2 consists of RNA determining the initial participation of innate immunity from receptors that identify ribonucleic acid. This pathway is initiated by the recognition of viral single-stranded and double-stranded RNA (dsRNA) via cytosolic RIG I-like receptors and extracellular and endosomal Toll-like receptors. Upon activation, these receptors trigger the secretion of type I, type III interferons, tumor necrosis factor alpha (TNF-α), and interleukins (IL) 1, 6, and 18[24]. The release of these inflammatory cytokines, such as IL-1Beta, in SARS-CoV-2 infection is determined by the activation of TLR-2, TLR-3 or TLR-4[25].

SARS-CoV interacts with MBL (Mannose-binding Lectin), a C-type lectin that activates MASP-2 (MBL-associated Serine Proteases) to cleave C4 and C2 and initiate the complement lectin pathway. The N protein of SARS-CoV-2 activates MASP-2 and potentiates C4b deposition in vitro[26].

Dendritic cells represent an important link between innate and adaptive immunity and can be divided into two types: immature and mature. Immature dendritic cells are migratory in the peripheral tissue, can capture antigen by endocytosis and transport it to the lymph nodes. These cells are equipped with RRPs that act as
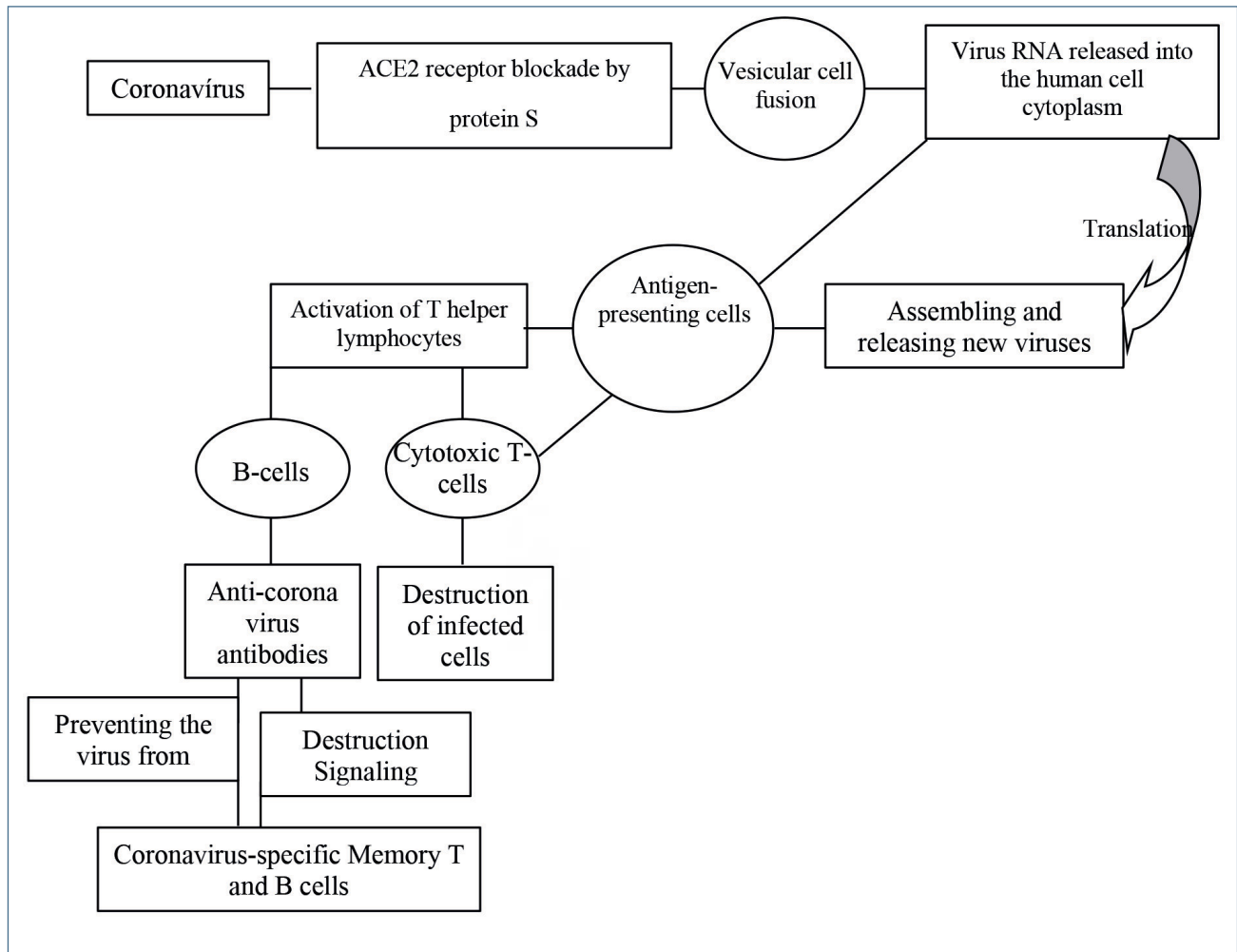
Figure 1: Mechanisms of SARS-CoV-2 infection and development of immunity. SARSCoV-2 binds to the ACE2 receptor via the S protein. Subsequently, the virus fuses with the cell and the viral RNA are released into the cytoplasm. New viruses start to be produced. Antigen-presenting cells activate T helper lymphocytes that can induce antibody production by the B cell and the destruction of infected cells by the cytotoxic T lymphocyte. Part of the antigen-stimulated T and B lymphocytes differentiate into long-lived memory cells, whose function is to mediate rapid and intensified responses to subsequent antigen exposure.

sensors for PAMPs[27] and induce the development of their mature phenotype, responsible for antigen presentation to T lymphocytes. Mature dendritic cells have high levels of MHC class II molecules and costimulatory molecules. In lymph nodes, DCs present antigen to CD4+ T lymphocytes[28] and simultaneously positively regulate the biosynthesis of CD40, CD80, CD83, and CD86, which bind to CD28 receptors present on Th0 lymphocytes, triggering the secretion of IL-12 or IL- 10 by DCs and differentiation of T cells into pro- or anti-inflammatory cells[29].

Decreased levels of dendritic cells and changes in their interaction with T lymphocytes represent an acute picture in SARS-CoV-2 infection, causing a lower rate of type I interferon release, decreased expression of chemokines and co-stimulatory molecules, delayed generation and expansion of helper and cytotoxic T lymphocytes, delayed differentiation of Th1 lymphocytes and their cytokines, and increased viral replication[30].

In intracellular infections, as in COVID-19, the antigen is presented to CD8+ T cells, which identify and destroy SARS-CoV-2 infected cells. CD4+ effector T cells can contribute to the activation of CD8+ T cells and B cells. CD4+ T cells are also responsible for the production of IFNγ, TNF and IL-2, which drive the recruitment of immune cells, intensifying the inflammatory process. In patients with SARS-CoV-2 infection, B-cell responses usually first emerge against the N protein and, within 4 to 8 days after the onset of symptoms, against the S protein[21].

In SARS-CoV-2 infection, the cytokines IL-1β and TNFα promote TH17-like response, characterized by the production of IL-17, GM-CSF (Granulocyte and Macrophage Colony Stimulating Factor), IL-21 and IL-22. IL-17 has broad pro-inflammatory effects with induction of G-CSF (Granulocyte Colony Stimulating Factor), causing granulopoiesis and neutrophil recruitment. IL-1β, IL-6 and TNFα, on the other hand, are responsible for inducing

inflammatory symptoms of a systemic character. In addition, IL-17 induces the following chemokines: KC (Keratinocyte Derived Chemokine), MIP2A (Macrophage Inflammatory Protein - 2A), IL-8, IP10 (Interferon Gamma-Induced Protein 10), MIP3A (Macrophage Inflammatory Protein - 3A), inducers of attraction and recruitment of more immune infiltrates, as well as matrix metalloproteinases that participate in tissue damage and remodeling. IL-21 is important in the maintenance of TH17 cells and in the STAT3 (Signal Transducers and Activators of Transcription-3) dependent germinal center responses. IL-22, aided by IL-17 and TNFα, induces antimicrobial peptides in mucosal organs and positively regulates mucins, fibrinogen, anti-apoptotic proteins, serum amyloid A and LPS3 (lipopolysaccharide) binding proteins. Consequently, IL-22 contributes to edema formation with possible associated morbidity and mortality[31].

Most patients with severe COVID-19 exhibit elevated serum levels of proinflammatory cytokines, including IL-6 and IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1 (Monocyte Chemoattractant Protein-1), MIP1α and TNF, a process characterized as cytokine storm[4].

Activation of the coagulation pathways during the immune response to infection also contributes to the overproduction of pro-inflammatory cytokines, leading to injury[32]. Defective procoagulant-anticoagulant balance predisposes to the development of microthrombosis, disseminated intravascular coagulation, and multiple organ failure, a process evidenced by the increased concentration of d-dimer in patients with COVID-19 pneumonia. Thus, the effects of coagulation activation significantly affect disease progression[33].

An interesting point in the pathogenesis of SARS-CoV-2 infection tends to be the significant reduction in the number of circulating lymphocytes. A decrease in CD4+ and CD8+ T-cell counts below the LLN (Lower Limit of Normal) has been described in severe and moderate cases. In addition, IFN-γ production by CD4+ T cells tends to be lower in severe cases than in moderate cases[34].

It is also worth noting that the difference in symptom severity and mortality rate associated with SARS-CoV-2 infection may also be related to the variation in the amount of perforin. A greater possibility of severe adverse effects is suggested to occur in adults over 70 years of age, obese individuals, and individuals with *Diabetes mellitus* (DM). The expression of perforin by cytotoxic T lymphocytes in these patients is reduced[35].

Differences in the severity of SARS-CoV-2 infection have also been attributed to the genetic variability of HLA (Human Leukocyte Antigen). Greater HLA variability of an individual allows recognition of various viral peptides potentiating the immune response and decreasing the severity of infection[36]. The profile of the number of cases and mortality rate that differs among countries or regions has drawn the attention of researchers about the clinical evolution of SARS-CoV-2 infection. In severe patients, lymphopenia, neutrophilia, decreased Treg lymphocytes, hyperreactivity, and exhaustion of CD4+ and TCD8+ T lymphocytes have been observed[37]. In this sense, understanding the immune response pattern, associating it with different degrees of disease, and identifying the mechanisms of virus-host interaction may represent possibilities for developing effective control methods against COVID-19.

Virus escape mechanisms

Evolutionarily, viruses have developed a series of mechanisms to escape the host immune system. Among the strategies are blocking viral recognition by the humoral immune response, interfering with the functioning of the cellular immune response, and altering the pattern of production of molecules and cytokines that are important in antiviral responses[38].

CoVs have also evolved mechanisms of evasion at various stages of innate immunity. SARS-CoV suppresses IFN release *in vitro* and *in vivo*, and SARS-CoV-2 likely has a similar effect. In fact, patients with severe COVID-19 demonstrate remarkably impaired IFN-I profiles compared to mild or moderate cases[24].

In SARS-CoV infection, to avoid RRPs, dsRNA is protected by membrane bound compartments that form during viral replication. In general, CoV infections, viral RNA is guanosine buffered and methylated at the 5' end by non-structural proteins (NSPs), resembling host messenger RNA (mRNA) to avoid detection by RLR[24].

Virus-encoded proteins avoid detection by the complement system, suggesting that their components are important for the antiviral response[39].

Another mechanism of immune response evasion is the viral protein encoded in the Open Reading Frame 8 (ORF8) of SARS-CoV-2, which shares the lowest homology with SARS-CoV among all viral proteins. It interacts directly with MHC-I molecules and negatively regulates their expression, decreasing the activity of cytotoxic T lymphocytes on cells expressing ORF8[40] (Figure 2).

The progression of the disease is directly related to the interaction of the various mechanisms of the new coronavirus with the immune system. Therefore, one can highlight the interaction with innate and adaptive immunity, activation of the complement system, expression and secretion of pro-inflammatory cytokines, activation of coagulation pathways, and even the escape mechanisms of this response as important factors for the outcome of the infection.

CONCLUDING REMARKS

Infection with the new coronavirus is recent and many of the associated factors are still uncertain. More concrete positions
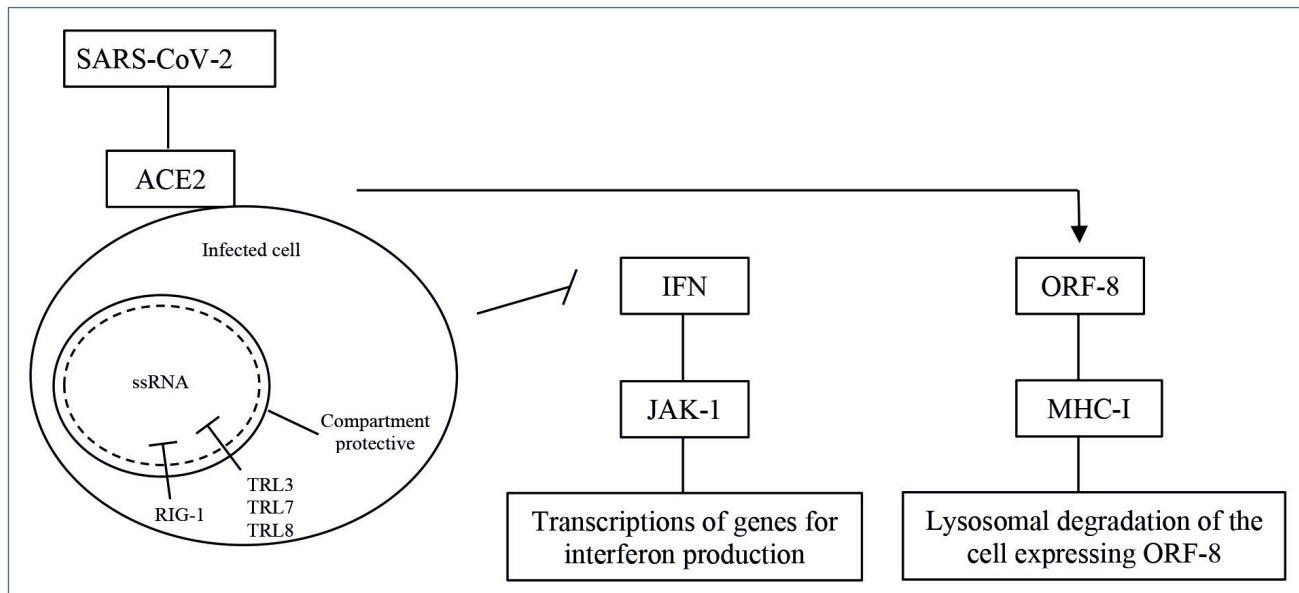
Figure 2: Main immune system escape mechanisms by SARS-CoV-2. After infecting the cell, SARS-CoV-2 develops escape mechanisms from the immune response. The dsRNA is protected by membrane-bound compartments that form during viral replication and prevent recognition by TRL-3, TRL-7, TRL-8, and RIG-1. Another mechanism of immune response evasion is the viral protein encoded in the open reading frame (ORF8) of SARS-CoV-2 that directly interacts with MHC-I molecules and negatively regulates their expression, decreasing the activity of cytotoxic T lymphocytes on cells expressing ORF8. SARS-CoV- 2 also induces an ineffective TNF response by altering gene transcription.

will be established as time goes on and the number of research studies increase.

This study described in a narrative and succinct way the main characteristics of SARS-CoV-2 and its association with immunological mechanisms. However, many studies need to be conducted in order to establish the participation of the immune system against COVID-19 in host defense, in the provision of biological markers for its detection, in the establishment of long-lasting protective immunity, and in the development of vaccine and drug controls. In addition, it is essential to evaluate the role of the immune system as a complicating factor, including the autoimmune character of the clinical manifestations.

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