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Immunoediting in SARS-CoV-2: Mutual relationship between the virus and the host

Nasim Kheshtchin [a,b], Parisa Bakhshi [c], Samaneh Arab [d,e], Maryam Nourizadeh [f,*]

[a] *Department of Immunology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[b] *Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[c] *Department of Medical Biotechnology, Faculty of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran*
[d] *Nervous System Stem Cells Research Center, Semnan University of Medical Sciences, Semnan, Iran*
[e] *Department of Tissue Engineering and Applied Cell Sciences, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran*
[f] *Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Immunoediting is a well-known concept that occurs in cancer through three steps of elimination, equilibrium, and escape (3Es), where the immune system first suppresses the growth of tumor cells and then promotes them towards the malignancy. This phenomenon has been conceptualized in some chronic viral infections such as HTLV-1 and HIV by obtaining the resistance to elimination and making a persistent form of infected cells especially in untreated patients. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a heterogeneous disease characterizing from mild/asymptomatic to severe/critical courses with some behavioral aspects in an immunoediting setting. In this context, a coordinated effort between innate and adaptive immune system leads to detection and destruction of early infection followed by equilibrium between virus-specific responses and infected cells, which eventually ends up with an uncontrolled inflammatory response in severe/critical patients. Although the SARS-CoV-2 applies several escape strategies such as mutations in viral epitopes, modulating the interferon response and inhibiting the MHC I molecules similar to the cancer cells, the 3Es hallmark may not occur in all clinical conditions. Here, we discuss how the lesson learnt from cancer immunoediting and accurate understanding of these pathophysiological mechanisms helps to develop more effective therapeutic strategies for COVID-19.

1. Introduction

Coronaviruses (CoVs) belonging to the Coronaviridae family, have caused three major zoonotic outbreaks in the past 20 years. After the outbreaks of severe acute respiratory syndrome CoV (SARS-CoV) in 2002 and Middle East respiratory syndrome CoV (MERS-CoV) in 2012 and 2015, faced a recent outbreak known as coronavirus disease (COVID-19) caused by a novel coronavirus strain called SARS-CoV-2 which was first identified in Wuhan (China) in December 2019. As it was rapidly spread across the globe, World Health Organization (WHO) declared COVID-19 as a pandemic on March 11, 2020 [1,2]. More than 250 million people have been diagnosed with COVID-19 and over 5 million died by the end of November 2021 [3].

Various studies have illustrated that the heterogeneity of COVID-19 and severity of disease are closely related to the virus itself, the hosts'

immune system, and the environment as a whole. Two arms of the immune system, the innate immunity involving monocytes, granulocytes, natural killer (NK) cells, and dendritic cells (DCs), and the adaptive immunity composed of T and B lymphocytes provide defense mechanisms against SARS-CoV-2. An effective immune function is crucial for an individual to suppress the virus and enter the recovery phase, while several factors including age, gender, malnutrition, and underlying diseases can affect the quality of the immune responses [1,4]. In such immunocompromised individuals, the virus is not easily removed, and the disease will progress to a severer phase. Manifestations of severe COVID-19 include lymphopenia with decreased numbers of $CD4^+$ and $CD8^+$ T cells, increased ratio of circulating neutrophils to lymphocytes, uncontrolled activation of neutrophils and lymphocytes leading to a massive release of a wide range of inflammatory cytokines, a condition known as cytokine storm which is a major cause of death in COVID-19

[5,6]. Therefore, increasing our knowledge on different aspects of cellular immune responses during the transition of patients from mild to a potentially fatal condition is highly required for improved diagnosis and applying the best therapeutic strategies.

Cancer immunoediting describes a dynamic process in which the immune system not only protects the body against tumor development but also shapes the immunogenicity of emerging tumors leaving behind subsets of tumor cells capable of escaping immune control. This occurs through three dynamic phases known as "3Es": elimination, equilibrium, and escape. The elimination indicates the process in which the elements of innate and adaptive immunity detect and destroy tumor cells, although some cells survive immune destruction and enter a dormancy phase or equilibrium. During the equilibrium phase, selection pressure of the immune responses results in the outgrowth of immunologically edited tumor cells. Then, the edited tumor cells enter the escape phase where they can uncontrollably progress, and become clinically detectable [7]. Recently, the capacity of occurring the immunoediting in untreated viral infections has been suggested, in which immunosurveillance is considered as a vital phase to control the early infection followed by an equilibrium between the virus-specific CTL responses and the infected cells that eventually leads to the escape of virus from antiviral immune responses [8]. Untreated HIV infection with a non-malignant escape phase which parallels the escape phase in tumors, and HTLV-1 as an oncogenic virus with a coordinated interaction between the virus and the host-mediated immune responses are two examples of viral infections resembling the immunoediting process in cancer. Immunoediting of the virus, was firstly hypothesized by Brad Jones et al, as a hallmark of viral infections with a latent period wherein long-lived infected cells undergo extensive clonal expansion and persist in anatomical sites that are usually inaccessible for effector cells. The concept of immunoediting in HIV-infected cells is based on the persistence of the cells expressing viral epitopes with escape mutations under the selective pressure of HIV-specific T cells and the available evidence on similarities between tumors and viral infections in terms of differential intrinsic susceptibilities to immunosurveillance [9,10]. According to recent reports, a crossroad of COVID-19 and cancer has been demonstrated to some extent due to similar clinical relevance including the cytokine storm, crucial role of type-I interferons (IFN-I), androgen-related severity of disease and aberrant regulation of immune checkpoint signalings. An immunoediting-like process has also been suggested in SARS-CoV-2 infection to help better understanding the virus behavior and to propose a treatment model [8]. Herein we discuss the fundamental knowledge of the phenomena and the possibility for SARS-CoV-2 to fit into immunoediting model through providing a detailed review of the literature and finding evidence for three distinct phases of immunoediting process in SARS-CoV-2 infection and suggest a non-cancerous escape phase for SARS-CoV-2 infected cells.

2. Cancer immunoediting

The idea that the immune system could control neoplastic disease was initially conceived by Ehrlich and approximately half a century later, in 1975, Burnet and Thomas proposed the cancer immunosurveillance hypothesis [11]. The immunosurveillance hypothesis was proved by various experimental studies and mainly based on the function of the adaptive immune system. Substantial amounts of data refined the concept considering both arms of the innate and adaptive immune system in sculpting the immunogenic phenotype of tumors [7,12]. In simplest form, tumors pass through each of three phases (3Es) of immunoediting sequentially, although transition or bidirectional manner is possible. External factors such as immune system aging and environmental stress might affect the process [12].

The original concept of cancer immunosurveillance can be assumed equal to the elimination phase. Because of the stromal remodeling that occurs during tumor growth, the innate immune system becomes alert, and it is the first step of the antitumor immune response. Releasing

chemokines at the site of tumor recruits more cells of the innate immune system which become activated following exposure to tumor antigens and cytokines, and finally help the adaptive immunity to completely eradicate the tumor cells. If the developing tumor is completely eliminated, the immunoediting process is finalized [7,13].

Equilibrium is probably the longest phase of 3Es and may be lasted for many years. In the equilibrium phase, the elimination of cancer cells by the immune system continues along with the emergence of the immune resistant variants. During the equilibrium phase, genetic instability and heterogeneity are the main resistance forces of tumor cells against the immune system[14].

Tumor cell variants that cannot be detected and eliminated through the two previous phases, progress into the escape phase. In the escape phase, tumor cells use various immune invasive strategies to evade the host's antitumor immune defenses towards an uncontrolled growth which makes them clinically detectable [7,12,15].

During these three phases of immunoediting, immune selection pressure plays a critical role in sculpting the tumor cells resulting in the selection of tumor cells with less- or non-immunogenic phenotypes. Several experimental findings indicate that lymphocytes such as CD8 + T cells and cytokines like IFN-γ play a major role in elimination of the immunodominant cancer cells and push the cancer cells to evade by inducing the upregulation of immune checkpoint molecules like PD-1 to support T cell apoptosis or imposing the escape strategies to the cancer cells including the loss of MHC class I and II antigens and decreased expression of tumor antigens [16]. Moreover, a double edge sward role of IFN-γ has been shown for IFN-γ-dependent pro- and anti-tumorigenic effects [17].

The concept of cancer immunoediting contains a complete integration between different functions of immune responses and tumor growth. Nevertheless, detailed identification of cellular and molecular mechanisms underlying the three phases of elimination, equilibrium and escape helps the scientists to develop new therapeutic approaches especially in the escape phase as an important hallmark of cancer.

3. Immunoediting in SARS-CoV-2

The concept of immunoediting is related to the gradual interaction between the immune system and a persistent factor like tumor cells or chronic infections. Most well-studied viruses develop chronic infections in a subset of patients [18] as evidenced in chronic Ebola infection being developed after acute infection [19]. The reservoirs of Ebola virus can be identified in tissues of infected individuals months or years after clearance of the virus from the blood. Viruses that cause chronic infections have developed a wide variety of strategies to ensure their long-term maintenance within the host's body. Viral integration, latency and persistent active replication are three mechanisms applied by different viruses to establish chronic infection in the host [20,21]. Accordingly, a chronic viral infection comprises distinct stages which parallel three steps of immunoediting process in cancer. The primary or acute stage is characterized by efficient recognition and eradication of infected cells by host's CD8+ T cells which results in the control of the viral replication (elimination phase). The chronic or latent phase implies a situation in which the virus remains in an equal situation with the host CTL responses for a long period of time (equilibrium phase) during which, the mechanisms of immune evasion are developed by the virus leading to a balance between the viral replication and elimination of infected cells by the host immune responses. This process eventually is followed by a progressive late-stage (escape phase) [9].

Multiple studies have found evidence on persistence of coronavirus infections resulting in chronic diseases. COVID-19 is a multisystem inflammatory syndrome with a very wide clinical spectrum [22]. While protective in the early phases of the disease, the immune responses contribute to disease severity and mortality via excessive proinflammatory cytokine release (cytokine storm) [22]. Although many SARS-CoV-2 infections resolve within 2–6 weeks, a growing number of

investigations show that in some COVID-19 patients referred to as "long-haulers" unsuccessful clearance of the virus from the body leads to developing a prolonged illness known as "long COVID"[23]. Moreover, recent studies highlighted the possibility of viral latency in different tissues such as brain, testis, and gastrointestinal tract through the detection of viral RNA and/or proteins [24–26].

Single-stranded RNA viruses such as hepatitis C virus (HCV) develop mechanisms to establish persistent infections. Such mechanisms occurs for protection of viral genome from being degraded by cellular ribonucleases or being recognized by innate immune receptors. Modifications at the 5′ and/or 3′ ends of the viral genomes is another strategy employed by RNA viruses to establish persistent infections [27,28]. As discussed later, infection by SARS-CoV-2, as an RNA virus, is accompanied by several immune evasion strategies which strengthen the viral infection capacity and weaken the control of infection due to impaired innate immune mechanisms including interferon responses and induction of cytokine storm. These events may define a role for immunoediting in SARS-CoV-2 reservoir persistence.

3.1. Elimination phase in SARS-CoV-2 infection

3.1.1. The effective role of innate immunity

Immunosurveillance is considered as a main potential feature of the immune system to detect and eradicate cancer cells and all other foreign invaders such as viruses, bacteria, and fungi. Antipathogenic effects of the immune system are initially begun through the generation of inflammatory mediators, recruitment of immune cells to the infection site, and induction of adaptive immune responses [29]. In the last two years since the pandemic began, numerous studies have been conducted on various mechanisms applied by the innate immune system to sense and defend against COVID-19 virus infection [6].

It is well documented that activation of pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain C-type lectin receptors (CLRs) by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) induce innate immune responses leading to secretion of interferons (IFNs) and proinflammatory cytokines [30].

Detection of the virus at the early stages of infection is essential in restricting virus replication. Recognition of SARS CoV-2 (as a single-stranded RNA virus) and subsequent activation of the immune responses can be achieved by the endosomal viral sensing PRRs (TLR-3, -7, and -8), and the cytoplasmic RLRs (RIG-I, MDA5, and NLRs). The recognition of viral PAMPS through PRRs activates different transcription factors including interferon regulatory factors (IRFs), the transcriptional regulators of type I (α/β) and type III (γ) IFNs as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) involved in the expression of immune-inflammatory cytokines and chemokines [31,32].

IFNs play a critical role in effective anti-viral responses through suppression of virus replication, stimulation of antiviral innate immune responses, and regulation of T cell expansion and memory induction. A recent study reported decreased plasma levels of IFN-α2, diminished serum activity of IFN-I, as well as down-regulation of IFN-stimulated genes in whole blood leukocytes of severe COVID-19 patients [33]. Lack of IFN-I or -III response to SARS-CoV-2 infection has been demonstrated in a culture model of the SARS-CoV-2 infection with primary human airway epithelial (pHAE) cells. In that in vitro model, the virus replication drastically decreased following pre-and post-treatment with the IFNs [34].

However, recent evidence shows a remarkable heterogeneity in IFN-I response between different cell types and different individuals concerning the amplitude and kinetics[6]. In vitro studies suggest an early transient wave of interferon-stimulated genes (ISG) upregulation in immune cells of COVID-19 patients, correlated with an early burst of IFN-α [35,36]. Further studies have demonstrated that the early peak of IFNs is followed by a declined concentration of IFN-α and IFN-λ in mild-to-moderate COVID-19 [37]. However, in severe patients, the IFN levels continue to increase particularly during the second week of onset associated with elevated levels of inflammatory cytokines such as IL-1, IL-6, CXCL8, and TNF-α [37]. These findings are consistent with the observations in a murine model of SARS-CoV-2 infection suggesting a pathological rather than protective effect for IFNs-I in severe patients [38]. The complicated dynamics of IFN response in patients with COVID-19 demonstrate the coordinated interaction between antiviral immune responses and proinflammatory mechanisms in early stages of the disease and in mild to moderate patients [6]. Here, we theorize that virus-induced events early in infected individuals are a major driver of the first step in immunoediting. Viral protein expression in infected cells promotes the presentation of viral antigens which activates immunosurveillance mechanisms resulting in the elimination of the virus. The early IFN response and its subsequent decline in mild to moderate patients could reflect the events of this stage.

In addition to IFNs, inflammatory cytokines and chemokines such as IL-1ß, IL-18, IL-6, CCL2, and CCL7 prevent virus replication. Some investigators have found that SARS-CoV viroproteins such as envelope (E) and 3a stimulate the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome that in turn triggers caspase cascade and subsequent production of inflammatory cytokines (IL-1, IL-18, and IL-6) [39,40].

Cells of both innate and adaptive immunity are predominantly involved in the elimination of SARS-CoV-2 in the early stages of viral infection. Innate immune cells including DCs, neutrophils, eosinophils, NK cells, monocyte, and macrophages are involved in the elimination of SARS-CoV-2 [41]. The critical impact of neutrophils as the early detectors of SARS-CoV-2 infection has been demonstrated according to the considerable increase in different factors including blood and bronchoalveolar lavage (BAL) neutrophil count, neutrophil to lymphocyte ratio (NLR), and neutrophil chemo-attractants in COVID-19 patients [42–44]. At the early stage, recruited neutrophils to the sites of infection fight the viruses through the phagocytosis pathway and the generation of reactive oxygen species (ROS) [45]. However, neutrophil-driven inflammatory pathways sometimes can lead to immunopathologic damage in patients [46]. Furthermore, pathogen-activated neutrophils are able to produce net-like structures known as NETs, composed of DNA-histone complexes associated with microbicidal peptides and oxidant enzymes. Several studies have speculated a central role for NETs formation in organ damage and death in COVID-19 patients [47]. NETosis is triggered by innate immune receptors following the recognition of microbial components and endogenous danger signals and must be strongly regulated to prevent tissue damage during acute or chronic inflammation and autoimmune disease [48,49].

In the other hand, macrophages play their important roles by detecting the viral danger signals through the PRRs, releasing several inflammatory molecules, and recruiting different effector cells to combat the viral infections [50]. As shown in previous reports, both monocyte-derived macrophages and tissue-resident alveolar macrophages in association with anti-SARS-CoV-2 antibodies are involved in eliminating the infected pulmonary cells in COVID-19 patients [51].

Dendritic cells as professional antigen-presenting cells (APCs) are known as central players in the initiation of adaptive immune responses, leading to elimination of viral infections [52]. Analysis of conventional dendritic cells (cDCs) in severe and mild COVID-19 patients illustrated a decreased expression of co-stimulatory proteins, MHCII, and TAP molecules and also increased levels of pro-inflammatory molecules including complement and coagulation factors in severely ill patients [53]. Moreover, plasmacytoid dendritic cells (pDCs) are known as IFN producers in the innate immune system. Increased activity of inflammatory and pro-apoptotic pathways have been shown in pDCs isolated from severe COVID-19 patients. In addition, a decrease in number and activity of pDCs was found in severe cases [54,55].

Eosinophils having potent pro-inflammatory functions are related to asthma and allergic diseases and involved in protection against parasites [56]. Furthermore, the protective effect of these cells has been demonstrated in some viral respiratory infections such as rhinovirus, respiratory syncytial virus (RSV), influenza, and *para*-influenza virus because eosinophils could restrict virus replication by the generation of nitric oxide (NO) via nitric oxide synthase 2 (NOS-2) [57]. Recent studies found lower eosinophil counts in peripheral blood of severe cases of COVID-19 infection, while increased eosinophil count is associated with a better prognosis. Therefore, eosinopenia can be applied as a prognostic factor for severe forms of COVID-19 patients [58]. However, it is assumed that eosinopenia may be the result of cell recruitments in the lung and intestinal epithelium as the main virus invasion locations [59,60]. In the monkey model of MERS virus infection, a huge amount of eosinophils infiltrated in the alveolar cavity, bronchi, and necrotic bronchial epithelial cells have been reported [61].

NK cells make an effective role in antiviral responses through both cytokine production and cell-mediated cytotoxicity [62]. It has been reported that SARS-CoV-2 infection induces a functional exhaustion phenotype in NK cells via upregulation of NKG2A, an inhibitory receptor that recognizes peptides presented by HLA-E molecules, as well as down-regulation of CD107a, IFN-γ, granzyme B, IL-2, and tumor necrosis factor (TNF)-α [63]. Evaluation of NK cell activity against SARS-CoV and SARS-CoV-2 revealed that spike 1 peptide presented by HLA-E molecules are detected by NKG2A receptors resulting in debilitating of NK cells [64]. In contrast, NKG2C as an activating receptor on NK cells, interacts with HLA-E on infected cells and can potentially limit the expansion of SARS-CoV-2 infection. In addition, an infiltration of a subset of memory'/activated CD57+NKG2C+ NK cells has been shown in some convalescent SARS-CoV-2 patients donors, as it has been previously found for CMV infections. [65]. Vietzen et al. reported that the severe form of COVID infection was associated with some specific alleles of HLA-E and NKG2C leading to NK cell response inhibition [66].

3.1.2. The effective role of adaptive immunity

T lymphocytes are considered as the major players in adaptive immune responses. The underlying mechanisms for eliminating the viruses include direct destruction of infected cells and also potentiating other immune cells like macrophages and B lymphocytes by producing effective cytokines. The central role of CD4+, CD8+ T cells, and B cells in the elimination of SARS-CoV-2 have been indicated in human and animal models. Of note, a higher viral load has been shown in CD4+ or CD8+ T cell-depleted mice [51]. The percentage of CD4+ and CD8+ T cells has been reported to be markedly decreased in severe COVID-19 patients and increased in survived patients when compared to those who were deceased [67]. Previous studies have demonstrated SARS-CoV-2-specific T cells and strong T cell memory responses in people with acute COVID-19 and in patients recovering from infection with and without antibodies. Memory cells are essential for long-lasting and protective immunity [68–70]. Humoral immunity contributes to antiviral responses mainly by producing neutralizing antibodies and inhibiting the virus entry into the host cells. Farshi et al reported that severe COVID-19 patients had lower B cell counts compared with mild cases, although both were within the normal range. Apparently, the significant role of humoral immunity is to prevent the SARS-CoV-2 invasion and cell entry and it is not able to eliminate the virus after the establishment of infection [51]. However, in hematologic cancer patients with COVID-19 positive results despite the impaired humoral immune response, increased numbers of antiviral CD8+ T cells provide effective protection and improve their survival [71,42]. The profile of the antibody response to SARS-CoV-2 is currently being investigated. It is well documented that IgM and IgA antibodies can be detected early in the first week, while IgG can be measured around 14 days post symptoms onset remains detectable up to 36 months [72]. Despite the fact that SARS-CoV-2 enters the body through the mucous membrane of the airways and secretory IgA (sIgA) is fundamental for the defense of the mucosa, little

attention was paid to the role of sIgA in COVID-19, [73]. The presence of SARS-CoV-2-specific IgA in serum of recovered patients and in the milk of breast-feeding mothers who recovered from the disease revealed in several reports [72,74,75]. However, it is not clear how long these blocking antibodies stay active.

3.2. Equilibrium phase in SARS-CoV-2 infection

As mentioned earlier, in the chronic or latent phase of viral infections which can be correlated with the equilibrium phase of the immunoediting process, there is a balance between antiviral immune responses and viral replication. During this stage, the virus develops several evasion mechanisms by which protect itself from being recognized by immune effector cells or interfere with the host's immune effector mechanisms. The function of the immune system now results in the selection of viral variants that are better suited to survive in an immunocompetent host. In the following section, we outline different evasion mechanisms employed by SARS-Cov-2 to persist in the host [9,10].

3.2.1. Genetic variation as an immune evasion mechanism

SARS-CoV-2 belongs to a genus beta-coronavirus with a positive-single-stranded RNA strand (Fig. 1). The size of the SARS-CoV-2 genome is about 29.9 kb and it shares approximately 78% sequence homology with SARS-CoV [76,77]. The two-thirds of the SARS-CoV-2 genomic RNA consists of two open reading frames (ORF1a and ORF1b) encoding pp1a and pp1b proteins which are finally cleaved into 16 nonstructural proteins (nsp): a papain-like protease (PLpro or nsp3), a 3C-like protease (3CLpro or nsp5) [78,79], an RNA dependent RNA polymerase (RdRp or nsp12), and nsp7- nsp8 co-factors [134,135]. The 3′ terminal one-third of the genome contains several genes encoding four structural proteins, including spike glycoprotein (S), envelope (E), nucleocapsid (N), membrane (M), and some accessory proteins [79,80]. The S protein covers the surface of the virus and is responsible for binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2) [81]. S protein is composed of two subunits named S1 and S2. The S1 consists of signal peptide (SP), receptor-binding domain (RBD), subdomain 1 (SD1), and subdomain 2 (SD2) while the S2 consists of heptad repeat (HR1-HR2), and fusion peptide transmembrane (TM) [82]. RBD is responsible for direct binding to ACE2 mediating the viral entry; thereby, serves as an important target for neutralizing antibodies (NAbs) [81].

From the first report of COVID-19 in China, different variants of SARS-CoV-2 have been emerging and diffusing around the world. Numerous types of mutations are involved in generating the new variants (Table 1). The mutations may alter virus characteristics, including antigenicity, infectivity, transmissibility, and pathogenicity. These variants have been classified in the context of 'variants of concern' (VOC) (Alpha, Beta, Gamma, Delta, and the recent variant named Omicron) and 'variants of interest' (VOI) (Epsilon, Eta, Theta, Iota, Kappa, and Lambda) by WHO and CDC. This list is likely to grow as new variants emerge. The rate of evolution of SARS- CoV-2 was approximately two mutations per month in the world population [83–85]. Various mechanisms of mutations, such as deletion, insertion, and substitution can alter the antigenic profile of the virus and are found in both the nonstructural (ORF1a and ORF1b) and structural proteins (N, M, and S). The most common types of the mistakes belong to the spike protein (RBD and NTD) which all increase the transmissibility [86].

Spike mutations are of great concern for the immune evasion of SARS-CoV-2. Epitope mapping approaches and serological analyses have revealed that these mutations result in increased affinity to ACE2 and escape from pre-existing NAbs which are from natural infection immunity or vaccines [85,87]. For instance, D614G, as the most frequent mutation in the spike, is common in all VOCs, highly infective, and resistant to NAbs [42]. The E484K substitution mutation facilitates immune evasion from both monoclonal and convalescent plasma antibodies [88,89]. Furthermore, the spike amino acid substitution
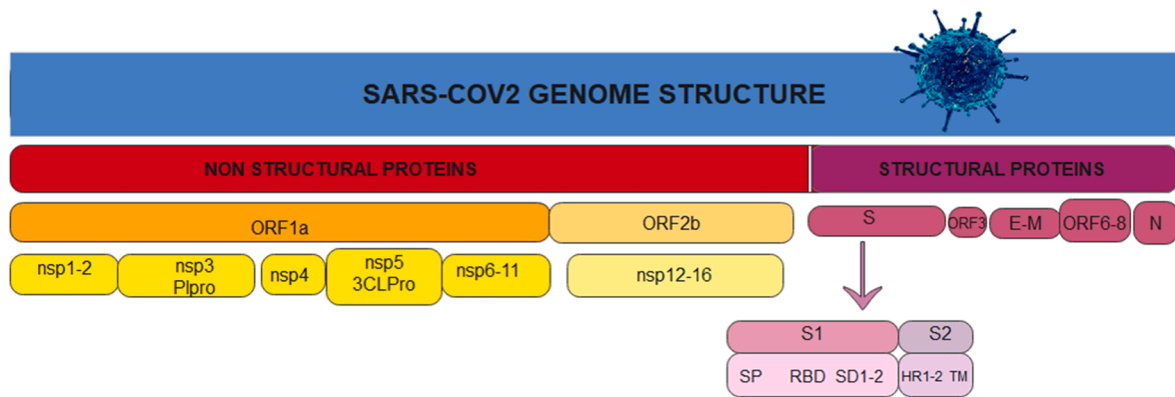
Fig. 1. The SARS-CoV-2 genomic structure.

Table 1

Variants of concern and location of the mutation in different domains in spike protein.

Label	Pango lineage	Location and key mutations in spike			First identified
Variants of Concerns (VOC)		NTD	RBD	S2	
Alpha	B.1.1.7	Del 69–70	N501Y	T716I	UK
		Del144Y	A570D	S982A	Sep 2020
			D614G	D1118H	
			P681H		
Beta	B.1.351	L18F	K417N	A701VI	South Africa
		D80A	E484K		May 2020
		D215G	N501Y		
		Del242-244	D614G		
		R246I			
Gamma	P.1	L18F	K417T	T1027I	Brazil/
		T20N	E484K		Japan
					Nov 2020
		P26S	N501Y		
		D138Y	D614G		
		R190S	H655Y		
Delta	B.1.617.2	T19R	K417N	D950N	India
		V70R	L452R		Oct 2020
		T95I	T478K		
		G142D	D614G		
		Del156	P618R		
		−157			
		R158G			
		A222V			
Omicron	B.1.1.529	A67V	G339D H	N764K	South Africa
		Del69-70	S371L	D796Y	Nov 2021
		T95I	S373P	N856K	
		G142D	S375F	Q954H	
		Del143-145	K417N	N969K	
		Del211	N440K	L981F	
		L212I,	G446S		
		ins214EPE	S477N		
			T478K		
			E484A		
			Q493R		
			G496S		
			Q498R		
			N501Y		
			Y505H		
			T547K		
			D614G		
			H655Y		
			N679K		
			P681		

mutations, K417N/T, and N501Y confer a stronger affinity for the ACE2 receptor [90,91]. Mutations, like deletion (shown as Δ) in NTD (ΔH69–V70, Δ243–244, ΔY144) have been demonstrated to abolish the neutralization [92,93]. Gene sequencing of the spike protein of Lambda

(a new VOI) showed six substitution mutations (G75V, T76I, L452Q, F490S, D614G, and T859N) and a single deletion (RSYLTPGD246-253 N). Among six mutations, three (G75V, T76I, and Δ246-253) are in the NTD, two (L452Q and F490S) are in the RBD, and the T859N is in the S2 subunit. Three mutations including the 246–253 deletion (Δ246-253) are located in an antigenic supersite and L452Q and F490S mutations markedly associated with antiviral immune evasion. Moreover, the T76I and L452Q mutations contribute to increased viral infectivity [94,95]. In addition, some gene errors can introduce an additional glycosylation motif that may mask the epitopes from antibody binding like human influenza viruses [96,97]. New variants are emerging throughout the globe, thus it is important to understand the role of specific mutations, both individually and in combination with other mutations.

The very recent variant, which named Omicron includes more than 30 mutations in its spike protein which is about three times more than the previous defined versions. It is not yet clear whether Omicron is more transmissible, or may causes more severe disease than previous variants, or whether it will make the vaccines less effective. In a new pre-print study released by the scientists from South Africa, they suggest a three times higher risk of reinfection with the Omicron strain than the previous variants[98].

Therefore, mutant variants may evade the immune system by at least three putative mechanisms: 1) stronger ligation to the ACE2 and 2) masking the epitopes by residual glycosylation, and 3) changing the binding sites by modifying the epitopes.

3.2.2. Evading the innate immune mechanisms by SARS-CoV-2

As mentioned above, innate immune responses and the antiviral IFN system serve as the first line of the defense against viruses which play crucial roles in limiting viral replication and promoting the adaptive immune responses [99]. Innate immune responses are initiated by recognizing viral PAMPs via PRRs [100]. Cytosolic RLRs including RIG-I, and MDA5, and endosomal TLRs mainly TLR-3, TLR-7, and TLR-8 are major PRRs responsible for detecting RNA virus infections such as coronaviruses and promoting the antiviral IFN pathway [101–104]. Ligand binding results in triggering the downstream adaptor proteins including myeloid differentiation primary response gene 88 (MyD88) and mitochondrial antiviral signaling protein (MAVS). Triggering adaptor proteins is followed by the activation of downstream kinases, TANK binding kinase 1 (TBK1), and inhibitor of κB kinases (IKKs) which then activate transcription factors IFN regulatory factor 3 (IRF3) and IRF7, and NF-κB upon phosphorylation. After translocation to the nucleus, activated transcription factors induce expression of type IFN-I and IFN-III [105]. Both IFN-I and IFN-III activate ISGs, through binding to IFN receptor (IFNR) on the cell surface, and subsequent activation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), leading to phosphorylation and binding of STAT1 homodimers and STAT1/2 hetero-dimers to the interferon-stimulated response elements (ISREs) located in

the promoter region of ISGs [102,106,107]. Most viruses express proteins that counter the innate immunity in different levels including inhibition of IFN production via interfering with PAMP recognition by PRRs or blocking the subsequent signaling pathways, hampering IFN downstream signaling cascades and finally interfering with host biological activities.

There is some evidence that coronaviruses including SARS-CoV-2 are capable of manipulating immune responses and have evolved several strategies to evade the innate immune responses especially through hampering the IFN induction and its subsequent signaling (Fig. 2) [108].

3.2.2.1. Evading the PRR-mediated viral sensing. Coronaviruses have developed multiple strategies to evade the host's innate immune responses by modifying or masking potential key antigenic epitopes to avoid being recognized by immune receptors. SARS-CoV-2 protects its RNA and proteins through replicating by replicase–transcriptase complex (RTC) which is associated with a complex vesicular network comprised of double-membrane vesicles (DMVs) [109]. DMV formation is commonly induced through coordinated function of multiple coronavirus nonstructural proteins, including Nsp3, Nsp4, and Nsp6, on the endoplasmic reticulum (ER) membrane [110]. Such ER-derived structures lacking PRR's, protect viral PAMPs from being exposed to cellular PRRs [110]. SARS-CoV-2 N protein binds the RNA and is responsible for

both the encapsidation of viral genome and creating aliquid–liquid phase separation to hide the viral RNAs from immune recognition [111,112]. It has been shown that N protein directly interacts with the RIG-I protein targeting the initial step of the IFN-β response [113].

Altered RNA modification signatures in the viral genomic RNA are another suggested strategy. The zinc-finger antiviral protein (ZAP), an interferon-induced mammalian enzyme, selectively binds to the CpG motifs of viral RNAs and degrades them. Many mammalian RNA viruses have evolved to lose their CpG motifs, thereby evading ZAP action which is associated with increased virulence. Interestingly, SARS-CoV-2 exhibits the most extreme CpG deficiency in all known betacoronavirus genomes [114]. Since CpG motifs are considered as PAMPs with the capacity to be recognized by host PRRs, decreased CpG content might be due to a selective pressure imposed by the host immune responses.

mRNAs of coronaviruses having a cap structure at their 5′ ends, mimic cellular mRNAs and are protected from being sensed by MDA-5 and the IFN-induced protein with tetratricopeptide repeats (IFIT) family proteins that target viral RNAs for degradation [115]. The viral RNA capping machinery is composed of Nsp10, Nsp12 [116], Nsp13, Nsp14, and Nsp16 [117–119], which work together to make viral RNAs indistinguishable from cellular mRNAs. Moreover, Nsp15, a conserved uridine-specific endoribonuclease encoded by coronaviruses, provides another mechanism to modify viral mRNAs which are likely used by SARS-CoV-2. Nsp15 is an integral component of the RTC that cleaves 5′-
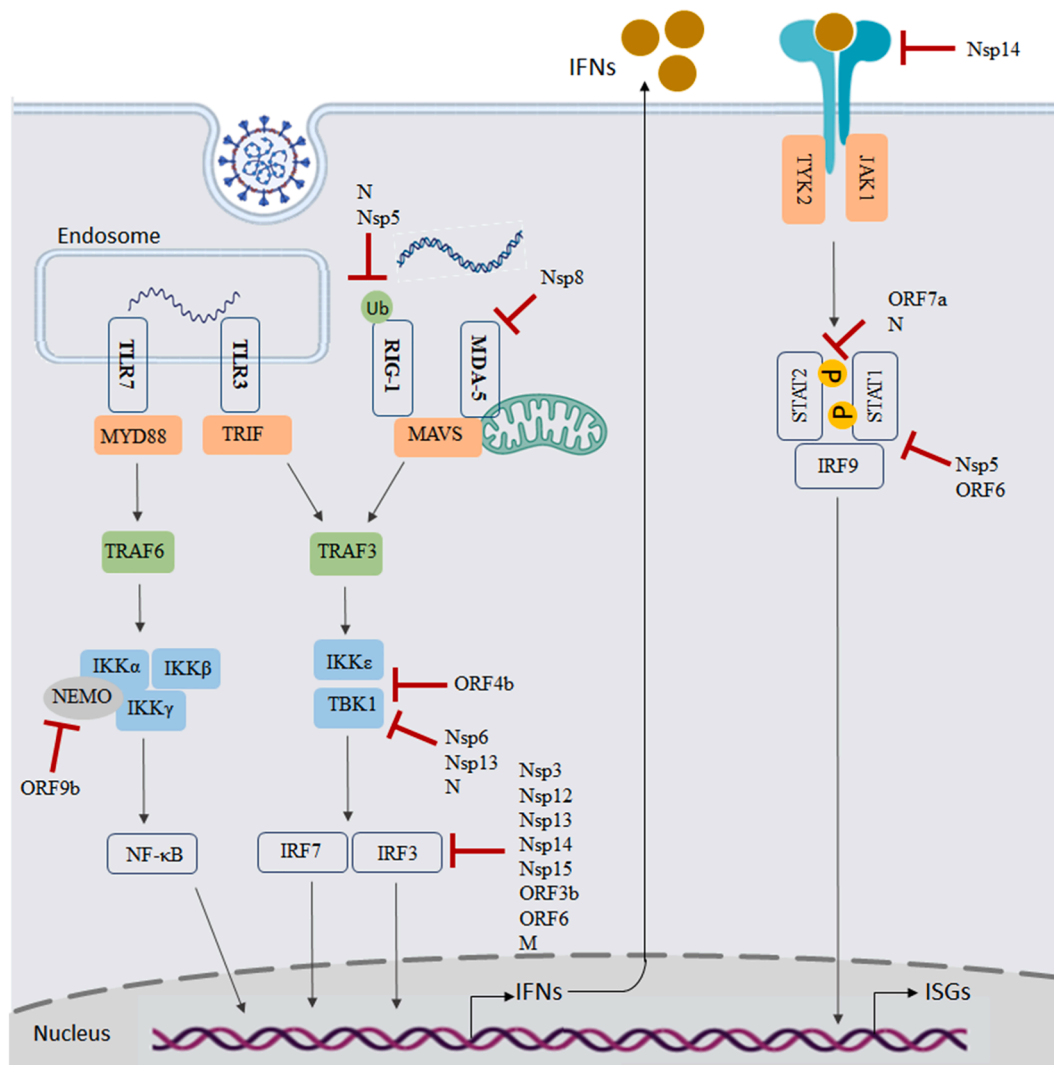

Fig. 2. Reported mechanism of innate immune evasion by SARS-CoV-2. Pathways of innate immune recognition (left) and interferon signaling (right), and reported mechanisms applied by SARS-CoV-2 to antagonize these pathways.

polyuridines from negative-sense viral RNA preventing the formation of dsRNA intermediates. As these components are sensed by cytosolic dsRNA sensors and promote host interferon response [120,121], this suggests a viral strategy to escape early events of host antiviral responses.

Modification of viral envelope proteins is another strategy utilized by coronaviruses to mask immunogenic viral protein epitopes or to enhance viral infectivity. Extensive glycosylation of the SARS-CoV-2 S glycoprotein has been evident by cryo-EM structure technique [122,123]. Modification of S protein glycosylation is another evasion mechanism applied by SARS-CoV-2 which allows new virus strains to resist against the neutralizing antibodies . In addition to S protein, other coronaviral proteins undergo modification by glycosylation, phosphorylation, palmitoylation, and ADP-ribosylation [124].

3.2.2.2. Evading PRR signaling and IFN production. Several SARS-CoV-2 proteins have been shown antagonize IFN responses with diverse mechanisms. Both IFN-I production and downstream signaling are inhibited by ORF6. ORF6 has been shown to be uniquely enriched at the nuclear pore complex (NPC) where interferes with the nuclear translocation of IRF3 and STAT1 through direct binding to the Nup98-Rae1 complex, leading to the shutdown of downstream events [125,126]. SARS-CoV ORF3b, a potent IFN antagonist, is localized in the mitochondria and involved in the inhibition of the MAVS-mediated IRF3 activation pathway [127]. Interestingly, SARS-CoV-2 ORF3b blocks IFN production more efficiently than the SARS-CoV ortholog due to a shortened C-terminal region. SARS-CoV-2 ORF3b also prevents IFN downstream signaling by blocking the IRF3 translocation into the nucleus [128]. NSP12, NSP13, NSP14, and NSP15 are other coronaviral proteins suggested to suppress IRF3 nuclear localization [129,130]. It has been reported that while Nsp13 inhibits TBK1 phosphorylation, Nsp6, another SARS-CoV-2 nonstructural protein, suppresses IRF3 phosphorylation through binding TBK1 without affecting its phosphorylation/activation status [131]. It has been shown that MERS-CoV ORF4b binds to both TBK1 and IKKε, preventing nuclear translocation of IRF3 [132]; such mechanism might be conserved in SARS-CoV-2.

The papain-like protease (PLpro) domain of SARS-CoV-2 Nsp3 cleaves interferon-stimulated gene 15 (ISG15) from IRF3 or cleaves IRF3 directly, dampening the IFN response [133]. Moreover, SARS-CoV-2 M protein antagonizes the induction of IFN-I and -III through interaction with RIG-I, MAVS, and TBK1, which interferes with the formation of the multiprotein complex containing RIG-I, MAVS, TRAF3, and TBK1 leading to inhibition of the phosphorylation, nuclear translocation, and activation of IRF3 [134,135]. It has been revealed that ORF9b encoded by SARS-CoV-2 associates with TOM70, a mitochondrial import receptor, which consequently prevents the recruitment of Hsp90 to TBK1/IRF3 and suppresses IFN-I responses [79,136]. ORF9b also inhibits IFN production through targeting the NF-κB essential modulator NEMO and interrupting its K63-linked polyubiquitination upon viral stimulation, leading to inhibition of the IκB kinase alpha (IKKα)/β/γ-NF-κB signaling [137]. SARS-CoV-2 N protein also interferes with the interaction between tripartite motif protein 25 (TRIM25) and RIG-I [138]. Moreover, the N protein restrains the association between TBK1 and IRF3, preventing the translocation of IRF3 into the nucleus [138]. SARS-CoV-2 Nsp5 might restrict IFN induction by reducing K63-linked ubiquitination on RIG-I [139]. It has been shown that Nsp8 could inhibit type I IFN signaling through direct binding to MDA5 and blocking its K63-linked polyubiquitination [140].

3.2.2.3. Evading IFN signaling pathway. SARS-CoV-2 also can use its structural and nonstructural proteins to evade the IFN downstream pathway resulting in diminished nuclear translocation of STAT1/STAT2. Nsp14 drives lysosomal degradation of type I IFN receptor, IFNAR1 [141]. As mentioned above, ORF6 interferes with the nuclear translocation of STAT1 through direct binding to the Nup98-Rae1 complex

[79]. Furthermore, SARS-CoV-2 Nsp1 inhibits IFN-I signaling by blocking STAT1 and STAT2 phosphorylation which is more efficient compared to SARS-CoV and MERS-CoV [131]. As discussed above, SARS-CoV-2 N protein antagonizes IFN induction via targeting the RNA sensing pathway. It has been shown that N protein also can act as an antagonist of IFN signaling by inhibiting the STAT1/STAT2 phosphorylation and nuclear translocation [142]. Nsp5, another SARS-CoV-2 nonstructural protein, prompts the autophagic degradation of STAT1 [139]. ORF7a of SARS-CoV-2 which is ubiquitinated at position Lys 119 (K119) inhibits IFN-α signaling by blocking STAT2 phosphorylation [143].

3.2.3. Evading host's intrinsic antiviral mechanisms

SARS-Cov-2 proteins also target intrinsic antiviral mechanisms within the cell to achieve their life cycles: Nsp1 of SARS-CoV and MERS-CoV suppresses host protein synthesis via induction of host endogenous 5'-capped mRNA degradation without affecting viral mRNAs [144]. Having a high amino acid identity with SARS-CoV Nsp1, SARS-CoV-2 Nsp1 may apply this mechanism to evade host immunity. SARS-CoV-2 Nsp1 also inhibits mRNA translation through binding ribosomal 40 s subunit and thereby preventing the assembly of the translation machinery. Indeed, Nsp1 C terminus binds to 40S ribosomal subunit and obstructs the mRNA entry tunnel, thereby, blocking antiviral responses triggered by RIG-I [145]. In addition, SARS-CoV-2 Nsp1 prevents mRNA nuclear transfer through interaction with the host mRNA export receptor heterodimer NXF1-NXT1, which is involved in nuclear export of cellular mRNAs, thereby subsequently suppressing protein synthesis [146,147].

Further investigations reported the direct interaction of several proteins of SARS-CoV-2 with mammalian proteins responsible for several biological processes. For example, Nsp5 interaction with epigenetic regulator histone deacetylase 2 (HDAC2), can affect the potential of HDAC2 to mediate the inflammation and interferon response through inhibiting the transport of HDAC2 into the nucleus[79]. Nsp8 and Nsp9 on the other hand, interfere with protein trafficking to the cell membrane through interaction with the 7SL RNA component of the signal recognition particle (SRP) complex [148].

It has been shown that SARS-CoV-2 N protein and Orf3a influence the host immune system by activating pro-IL-1β gene and IL-1β secretion, leading to the induction of NF-kB signaling and NLRP3 inflammasome and generation of cytokine storm[71,149]. ORF3a also regulates apoptotic pathways. Apoptosis is a double-edged sword in the pathogenesis of viruses. Considering apoptosis as a host defense mechanism, some viruses including SARS-CoV-2 encode anti-apoptotic proteins that provide a sufficient time for viral replication. In contrast, some other types of viruses such as influenza and HIV apply apoptosis to exit the cells, spread throughout the tissue, and infect other cells which are also considered as the hallmark of SARS-CoV-2. Recent studies have shown that SARS-CoV-2 ORF3a activates host cell apoptosis through the extrinsic pathway in which caspase-8 cleaves Bid to tBid, leading to the release of cytochrome *c* from the mitochondria and subsequent formation of apoptosome and caspase-9 activation [71,150]. As previously indicated, cell death can be considered as an escape mechanism allowing the release of more particles and helping the virus to further spread throughout the epithelium and lung. However, caspase-8 mediated apoptosis and especially necrosis as an immunogenic cell death pathway restricts the virus through not only eliminating the virus-infected cells but also stimulating the innate and adaptive immune responses for limiting the viral replication [151]. Finally, Orf3a is involved in the lysosomal pathway through inhibition of autophagy by blocking fusion of autophagosomes/amphisomes with lysosomes [152] while, ORF7a interferes with autophagosome acidification [141,152]. Another escape strategy of SARS-CoV-2 has been indicated through the direct intraction of ORF8 with MHC-I molecules which results in the lysosomal degradation of MHC-I molecules with a mechanism known as autophagy. Down-regulation of MHC-I molecules impairs an appropriate antigen presentation which is required for recognizing the infected cells and a

complete killing function of cytotoxic T lymphocytes [153]. ORF6 protein, on the other hand, inhibits MHC class I expression through suppression of STAT1, IRF1, and NLRC5, the key transcriptional regulators of MHC-I expression [154]. Targeting NLRC5 by cancer cells through mechanisms including genetic mutations, loss of NLRC5 gene copy numbers or promoter methylation to evade anti-tumor immune responses has been shown in different tumors. Regarding similar evading approaches in some viruses and cancer cells, the disease severity and mortality in COVID-19 patients might be associated with the expression level of NLRC5 [155].

3.3. Escape phase in SARS-CoV-2 infection

In patients with fatal COVID-19, a dysregulated immune response results in extensive damage to the lung and other organs and eventually to death. As described in the previous section, SARS-CoV-2 develops multiple inhibitory mechanisms against the host immune system among which are several strategies to inhibit IFN pathways leading to defective clearance of the SARS-CoV-2. The absence of IFN production or sensing, persistence of the viral infection, prolonged exposure to PAMPs, as well as the release of DAMPs, lead to the activation of several innate immune pathways including persistent hyperactivation of the monocyte and macrophage [156,157]. In critical COVID-19 patients, macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (HLH) as well as a decreased number of different types of lymphocytes is accompanied by a systemic inflammatory response known as cytokine storm. The cytokine storm is characterized by hyperproduction of an array of pro-inflammatory cytokines and chemokines including IL-2, IL-6, IL-7, IL-8, IL-10, TNF-α, IFN-γ, G-CSF, GM-CSF, and MCP1 [158]. The evidence suggests a direct association between aggressive proinflammatory cytokine release with lung injury, multiorgan failure, and poor prognosis of severe COVID-19 [159,160]. Interestingly, the serum level of IL-6 shows a strong correlation with disease mortality [161,162]. As in tumors and other chronic viral infections, persistent inflammation or viral infection accompanied by high levels of inhibitory IL-10 can cause immune exhaustion in immune cells, particularly in T cells. Effector cytotoxic cell populations including NK cells (responsible for primary control during acute viral infection) and CD8 + T cells (critical mediators for long-term surveillance) display a terminally differentiated/senescent phenotype, poor cytotoxic response as well as reduced capacity to produce antiviral cytokine [163,164]. Interestingly, the correlation between diminished cytotoxic potential and serum levels of IL-6 suggests a direct/indirect role for this cytokine in the impairment of cytotoxic lymphocytes. Increased expression of perforin and granzyme A in NK cells following IL-6R treatment provides further evidence for this assumption [164]. Chronic inflammation due to a sustainable low-grade production of pro-inflammatory cytokines, such as TNF-α and IL-6, directly promotes the ARDS and influence the severity of COVID-19. This situation is of a particular significance in patients with underlying conditions like obesity and type 2 diabetes who are at a higher risk of COVID-19 complications and even mortality [165]. Leptin as a hormone predominantly made by adipose cells and a regulator of the immune system, has pro-inflammatory properties and upregulates the secretion of inflammatory cytokines like TNF-α, IL-6, and IL-12. Moreover, dysregulated function of classically-activated-macrophages (M1) in adipose tissue and impaired type I IFN production worsen the survival rates in COVID-19 patients with obesity [166,167].

Taken together, a dysfunctional immune response characterized by decreased lymphocytes numbers, hyper inflammation, impaired cytotoxic response, and immune exhaustion leading to increased viral load is observed in COVID-19 patients [168]. Aberrant or exaggerated response of the host's immune system can lead to severe disease and even death if treatment is not adequate. Indeed, the outcome of the infection is affected by both the host's immune response and viral factors. Immune response dysregulation is at least in part related to immune inhibitory

strategies applied by the SARS-CoV-2. Most patients with poor prognostic features upon hospital admission eventually encounter complications with acute respiratory distress syndrome (ARDS), acute renal injury, multiorgan failure, and blood clots [161,169].

4. Current therapeutic options for treatment of COVID-19

Since the onset of COVID-19 pandemic, tremendous efforts have been made to identify safe and effective drugs against SARS-CoV-2. Different pharmaceutical interventions have been suggested based on the interplay between the virus and the host immune responses. One potential approach would be the use of components preventing the receptor recognition thereby blocking entry of the virus to the host cells. Such approaches include antibodies targeting SARS-CoV-2 S protein or a recombinant soluble form of ACE2[170–173]. The endocytic pathway which enables entry of the virus after receptor recognition has been targeted in several studies by endosomal-tropic agents such as hydroxychloroquine sulfate or umifenovir[174]. However, once the cells were infected the rapid replication of the virus within the infected cells will drive the manifestations of the disease. In this regard, SARS-CoV-2 RNA polymerase (Nsp12-RdRp), a key enzyme for viral replication and mutagenesis, is a target for designing antiviral treatments. Favipiravir and remdesivir, two nucleoside analogues, act via inhibition of RdRp and remdesivir was the first FDA-approved drug for COVID-19 [175,176].

As indicated, uncontrolled viral replication as a result of viral evasion of host's immune mechanisms together with excessive release of proinflammatory cytokines leads to the tissue and organ damage. Targeting the key molecular players in signaling pathways which are altered by the viral infections is another treatment strategy. IFNα-2b, an FDA-approved recombinant interferon alpha-2 protein for treatment of several cancers, also interferes with viral replication and promotes antiviral activities of immune cells through binding type-1 interferon receptors[177,178]. IFNα-2b is currently under clinical trials for treatment of COVID-19. Clinical evidence indicates the potential effects of anti-inflammatory and immunosuppressive treatments for COVID-19. Monoclonal antibodies against inflammatory molecules or their receptors including tocilizumab, sarilumab, siltuximab (inhibitors of IL-6 receptor), gimsilumab (GM-CSF inhibitor), and fingolimod (a sphingosine-1-phosphate receptor modulator) have been suggested to reverse the uncontrolled inflammatory response in severe COVID-19 patients through inhibition of inflammatory cytokines or trafficking of the immune cells[179]. Administration of corticosteroids including prednisone, methylprednisolone and dexamethasone have been shown to have substantial benefits in late stage disease suppressing the pulmonary inflammation; however, their use can interfere with antiviral immune responses in the early phases of the disease[180].

To date, none of the investigated drugs for COVID-19 in clinical trials, demonstrated to be clearly effective. Therefore, a thorough understanding of the SARS-CoV-2 behavior in the host and its interaction with immune mechanisms would provide insights to develop more effective therapeutics.

5. Concluding remarks

The plentiful experimental and clinical evidence on the existence of immunoediting process from immune surveillance to escape in cancers have guided the scientists to develop new treatment strategies by targeting the critical molecules involved in sculpting the tumor cells such as IFN-γ and immune checkpoints (PD-1 and PD-L1) . Regarding the initial contribution of the immune system to eliminate the virus-infected cells, the immune evasion mechanisms developed by the virus may result in making the virus invisible to the immune recognition or its localization in anatomical sites that are poorly accessible to the immune cells. COVID-19 is a heterogeneous disease with many knowledge gaps and ambiguities about the mutual interaction of virus-infected cells and

the immune system, duration of the infection, and the time of complete clearance of viruses from the body. Among those who recover from COVID-19, some develop persistent symptoms for months, a condition referred to as long COVID. The persistence of SARS-CoV-2 in certain tissues, evidenced by some investigations, is one of the suggested contributors to long COVID [24–26]. In such patients the role of the immune system in exerting immune selection pressure on virus infected cells through the mechanisms of immunoediting might be involved in the persistence of the disease. However, the immunoediting in SARS-CoV-2 infection might not exactly resemble the process in cancer regarding uncontrolled immune responses in COVID-19 and different potential factors contributing to the development of long COVID. Understanding the exact effectors in immune processes involved in immunoediting in SARS-CoV-2 infection may provide promising approaches to design immunotherapeutic strategies to overcome the evading mechanisms and harnessing the hyperactivated immune responses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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