Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Immunopharmacology 112 (2022) 109183

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Molecular mimicry, hyperactive immune system, and SARS-COV-2 are three prerequisites of the autoimmune disease triangle following COVID-19 infection

Maedeh Vahabi, Tooba Ghazanfari *, Saeed Sepehrnia

Immunology Department, Immunoregulation Research Center, Shahed University, Tehran, Iran

ARTICLE INFO

Keywords:
Molecular Mimicry
Hyperactive Immune System
SARS-COV-2
Autoimmune Disease

ABSTRACT

SARS-CoV-2 infection can produce a variety of clinical manifestations, which are either directly related to viral tissue damage or indirectly induced by the antiviral immune response. Molecular mimicry enables this virus to undermine self-tolerance in a host's immune system also immune system's attempts to eliminate SARS-COV-2 may trigger autoimmunity by hyper-activating the innate and adaptive immune systems. Auto immune diseases include Systemic lupus erythematosus, autoimmune thyroid diseases, Guillain-Barre syndrome, Immune thrombocytopenic purpura, and the detection of autoantibodies are the cues to the discovery of the potential of COVID-19 in inducing autoimmunity. As COVID-19 and autoimmune diseases share a common pathogenesis, autoimmune drugs may be an effective treatment option. Susceptible patients must be monitored for autoimmune symptoms after contracting CVID-19. In light of the SARS-COV-2 virus' ability to induce autoimmunity in susceptible patients, will the various COVID-19 vaccines that are the only way to end the pandemic induce autoimmunity?

1. Introduction

Pathogen infection and autoimmune disease' may imply that pathogens are suspected of causing autoimmune diseases. Pathogens of all kinds, including viruses, bacteria, and parasites, can cause direct damage to organs and tissues, which stimulates the body's immune system to destroy the foreign invader. As a consequence of pathogen infections, several inflammatory cascades occur that result in the attraction, differentiation and expansion of cells of the innate and adaptive immune systems. A number of mechanisms have also been implicated in the breakdown of self-tolerance, including molecular mimicry [1], epitope-spreading [2], superantigen production [3], direct cytotoxicity [4], Innate immunity activation [5], persistent or recurrent viral infection[6] bystander activation, pathogen-induced necroptosis, and cross-linking or molecular mimicry [7,8]. New evidence on type 1 diabetes (T1D) pathogenesis highlights the role of recurrent viral infections in autoimmunity. Different types of viral infections such as coxsackievirus B (CVB) [9,10] cytomegalovirus (CMV), and enteroviruses [11,12] have been postulated to be associated with type 1 diabetes. Systemic lupus erythematosus (SLE), as the most common type of lupus has been suggested to be associated with hepatitis C virus (HCV) [13,14], CMV [15], dengue virus [16], parvovirus B19 [17], EBV [18,19] and Torque Teno Virus (TTV) [20]. Furthermore, Epstein-Barr virus (EBV) [21,22] Measles virus [23], and Varicella-zoster virus (VZV) [24,25] have been attributed to triggering the immune system to attack the brain and spinal cord, thereby leading to Multiple Sclerosis(MS) (Table 1).

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome (SARS) associated coronavirus 2 (SARS-CoV-2). While most infected individuals are asymptomatic, some develop severe diseases involving multiple organs with COVID-19 [26]. Certain medications used to treat autoimmune rheumatologic diseases may have therapeutic effects in patients with severe COVID-19 infections, highlighting the link between COVID-19 and autoimmune disease [27,28]. SARS-CoV-2 may also trigger autoimmune disorders in genetically predisposed people [29].

2. A major mechanism for triggering an autoimmune reaction by SARS-COV-2 is molecular mimicry

One of the mechanisms by which infectious or chemical agents induce autoimmunity is through molecular mimicry. A foreign-derived antigen activates autoreactive T and B cells in a vulnerable individual when peptides derived from foreign and self-peptides have similarities. Additional links to our understanding of molecular mimicry include host

* Corresponding author.

https://doi.org/10.1016/j.intimp.2022.109183
Received 7 June 2022; Received in revised form 9 August 2022; Accepted 17 August 2022
Available online 22 August 2022

Table 1
Autoimmune conditions associated with viral infection.

Associated autoimmunity	Virus	Mechanism	Reference
T1DM	CVB	Superantigen production/ Direct cytotoxicity	[9,30]
	CMV	Persistent or recurrent viral infection	[6]
	enterovirus	Innate immunity activation/ Persistent or recurrent viral infection/ Superantigen production	[6,10,31]
SLE	HCV	Epitope spreading	[13,14]
	CMV	Epitope spreading	[15]
	Dengue virus	Epitope spreading	[16]
	Parvovirus B19	Molecular mimicry	[17]
	EBV	Molecular mimicry, epitope spreading	[19,32]
	(TTV)	Molecular mimicry	[20]
MS	EBV	Bystander activation/ Persistent or recurrent viral infection/ Molecular mimicry	[21,33]
	Measles virus	Epitope-spreading/ Direct cytotoxicity	[23,24]
	VZV	Persistent or recurrent viral infection/	[24,25]

Abbreviations: T1DM, type 1 diabetes mellitus; CMV, cytomegalovirus; SLE, systemic lupus erythematosus; HCV, hepatitis C virus; MS, multiple sclerosis; EBV, Epstein-Barr virus; VZV, varicella-zoster virus.

genetics, microbiota exposure, and environmental chemicals [34]. Molecular mimicry has been proposed as a cause of the autoimmune phenomena observed in COVID-19 [35,36]. As a result of analyzing tissues from COVID-19 victims, they identified cellular and molecular patterns that lead to the damage of epithelial and other structures resulting in death, which underscores the role of autoimmunity brought on by molecular mimicry in the pathology of COVID-19 [37]. Another study supported this idea, that self-reactivity against proteins involved in activation/development of B- and *T*-cells can be explained by molecular mimicry. Moreover, accordingly, the extent of immunosuppression is determined by the extent of immune responses themselves. An immunosuppression that is more severe is caused by cross-reactions against human immunodeficiency–related proteins when the immune response triggered by SARS-CoV-2 immunization is higher. As a result, SARS-CoV-2-induced immunosuppression can be considered a molecular mimicry syndrome [38].

The autoimmune theory is supported by many clinical reports from covid-19 patients. Some have suggested that molecular mimicry may be responsible for immunological cross-reactivity between viral and human molecules, and thus play a role in the generation of autoimmunity in COVID-19 [35,39]. In addition to being highly conserved, heat shock proteins (many of which are molecular chaperones) are capable of intracellular localization [40,41], and the introduction of autoimmunity caused by antigenic epitopes responding to microbial chaperones has already been documented in various diseases as well as the immune response [42,43].

One study compared amino acid sequences of all SARS-CoV-2 proteins with heat shock proteins, many of which are molecular chaperones, to see if they share amino acids with antigenic potential, which can elicit cross-reactive antibodies and effector immune cells capable of damaging and destroying cells by autoimmunity [44]. A sequence analysis of 20,365 human proteins revealed 3781 proteins with at least six amino acids (≥6 mer) similar to SARS-CoV-2 proteins, and 17 of those are molecular chaperones. 17 human chaperones and viral proteins share peptides that are likely to trigger an autoimmune reaction if recognized by the human immune system. Stress (shear and/or metabolic) associated with COVID-19 causes chaperone molecules to translocate from their intracellular location to the plasma-cell membrane and extracellular space, which results in autoimmunity [44].

3. Hyperactivation of the immune system during covid-19 infection

There is no doubt that viruses can trigger or exacerbate autoimmunity in genetically predisposed individuals, likely by aberrantly activating immune pathways involving either the innate or adaptive immune system.In covid-19 infection the innate and adaptive immune systems attempt to eliminate the virus, the virus sometimes interacts with the body in a way that stimulates immune and non-immune cells, leading to a hyperactive immune response [45].

Some patients experiencing severe COVID-19 develop an overactive cytokine storm or "cytokine release syndrome" characterized by the release of cytokines from macrophages, dendritic cells, and monocytes, such as interleukin 1 (IL1) and interleukin 6, interleukin 10 (IL10), tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β) and ferritin [46,47]. The presence of these cytokines causes eosinopenia and lymphocytopenia characterized by low numbers of eosinophils, CD8+ T cells, natural killer (NK) cells, and nave *T*-helper cells, while simultaneously activating nave B-cells, increasing *T*-helper cell 17 (Th17) lymphocyte differentiation, and stimulating monocyte and neutrophil recruitment. An acute respiratory distress syndrome (ARDS) results from a generalized, nonspecific hyperinflammatory response in the lungs with consequent activation of nonspecific inflammatory response in the circulatory system and other organs, sometimes leading to multiorgan failure, leaky vasculature, coagulopathies, or strokes [48,49].

4. The role of innate immunity in triggering an autoimmune response in SARS-CoV-2 infections

For any new infection, the initial immune response is provided by the innate immune system, which is highly visible in both respiratory and intestinal mucosa, and continuously seeks out and counteracts potential threats through a complex interaction of cells and soluble mediators [50]. In addition, resident macrophages and monocytes, natural killer (NK) cells, innate lymphoid cells, polymorphonuclear and dendritic cells, and cytokines, chemokines, and the complement system all participate in the process [51].

4.1. Toll-like receptors (TLR)

During cytokine storms, cytokines are released by the cells of the innate immune system in response to pathogen-associated molecular pattern molecules (PAMPs) that identify microbes and distinguish them from host antigens. These innate cells recognize PAMPs through many receptors, including Toll-like receptors (TLR), nucleotide-oligomer domain-like receptors (NLR), NLR family pyrin domain-containing proteins (NLRP), retinoic acid inducible gene 1-like receptors (RIG or RLR), and melanoma differentiation-associated protein 5 (MDA5), among others. Based on whether they exist on the cell membrane (TLRs 1, 2, 4, 5 and 6); within cells on endosomal membranes (TLRs 3, 7, 8, 9 and 10) or within the cytoplasm (NOD1, NOD2, RIG1, MDA5 and NLRP3), TLRs and NLRs can be divided into three groups [52] (Figure 1, A).

There are potentially a number of TLRs that participate in COVID-19 infection, such as TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, and TLR9.We should also consider both the beneficial and harmful effects of TLRs when dealing with COVID-19 infection. The TLRs could be used to control the infection in the early stages of disease, however; it can also harm the host due to persistent inflammation and tissue destruction [53]. Type 1 IFN plays an important role in SARS-CoV-2 as the production of type 1 IFN is mediated by TLRs, they could play a crucial role in COVID-19 disease. An infection with COVID-19 could activate the

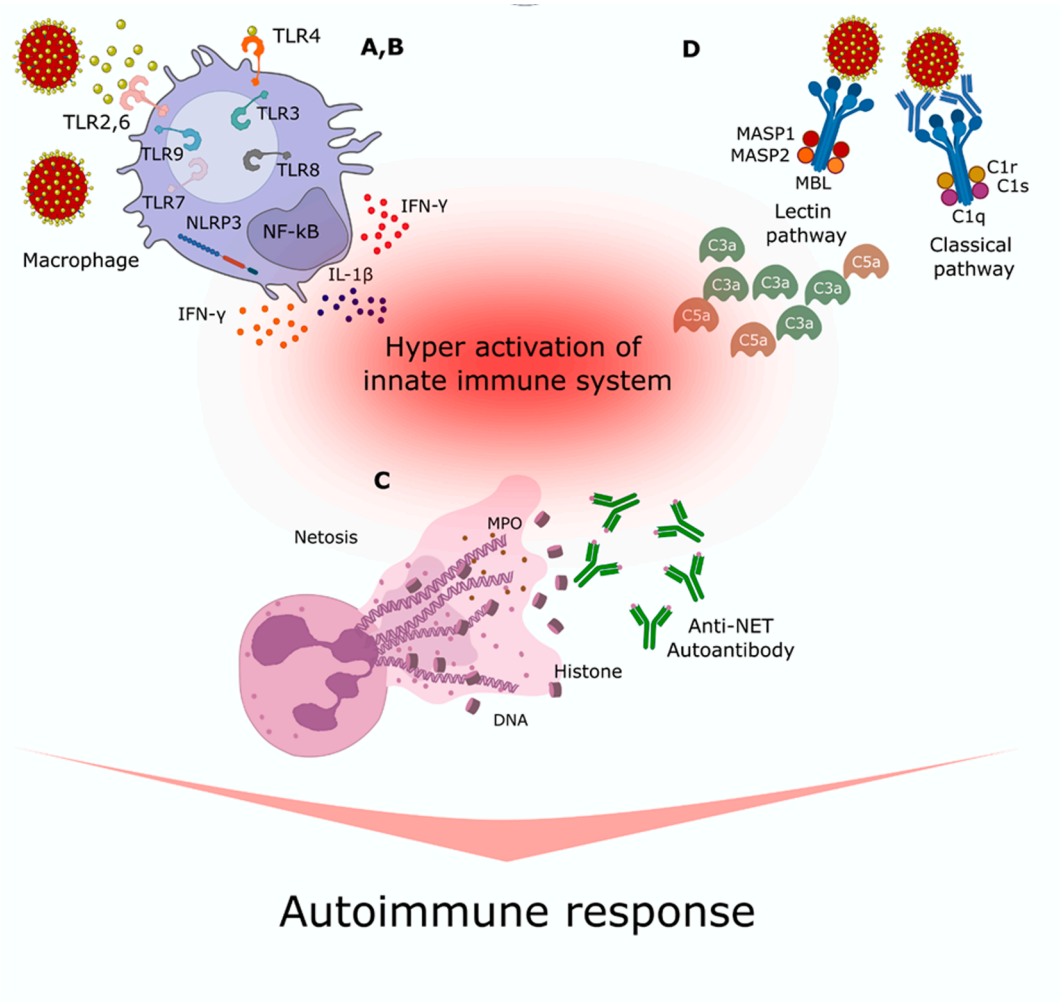

Fig. 1. SARS COV-2 virus can hyperactivate the arms of the innate immune system.
When these innate immune pathways are over-activated by SARS COV-2, a wide range of cytokines are released, which ultimately cause uncontrolled inflammation and autoimmune responses. **A, B.** The monocyte-macrophage system is controlled by pattern recognition receptors, including the endosomal toll-like receptors (TLR), and the nucleotide oligomerization domain-like receptors (NLR) that helps trigger an antiviral response, mainly explicated through the production of IFNλ. Viral proteins and nucleic acids can activate the inflammasome platforms in cells belonging to the monocyte-macrophage system with the following production of IL-1 and IL-18. **C.** Neutrophils release a number of active molecules when they form NETs, including cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and histone H3 citrulline (Cit-H3), which increase the concentration of these autoantigenes in plasma, leading to autoantibodies against the NETs. **D.** The SARS COV-2 can activate classical, and mannose-binding protein pathways, which are products of both C3a and C5a pathways. Dysregulation of the complement system can result in an imbalance between the host's defenses and the inflammatory response.

TLRs, leading to the production of pro-inflammatory cytokines, such as IL-1β and type 1 IFN [54] Many autoimmune diseases, such as systemic lupus erythematosus (SLE) [55], primary Sjögren's syndrome (SS) [56], Kawasaki syndrome,and behcet's disease [29] are characterized by hyper-production of IFN (mainly type I), which may be linked to primitive viral infections [57,58].

Other studies on SARS-CoV2 have indicated that excessive inflammation resulting in NETosis and inflammasome activation is caused by excessive TLR4 activity in COVID-19 patients [59,60]. In addition, TLR agonists could be used as prophylactic drugs for SARS-CoV-2 [61].

4.2. The inflammasome pathway

In addition to IFN response, viral proteins and nucleic acids can lead to systemic pro-inflammatory effects through IL-1 and IL-18 production after activation of the inflammasome system in cells belonging to the monocyte-macrophage system [62]. As well as RNA viruses, viral pathogen-associated molecular patterns (PAMPs) of RNA viruses, including SARS-CoV-2, can activate pyrin-containing NOD receptor 3 (NLRP3), while their RNA fragments can activate RIG-I, MDA5, and the mitochondrial antiviral signaling pathway (MAV).Through intranuclear translocation of nuclear factor kB (NF-kB), transcription of pro-IL-1 and pro-IL-18 genes, and the conversion of these precursors into active cytokines through inflammasome-driven caspases, these events culminate in the production of pro-inflammatory cytokines such as IL-1 and IL-18 [58].(Figure 1.B) Through activation of NLRP3 inflammasomes and the release of pro-inflammatory cytokines from cells through Gasdermin-pores commonly found in cell death by pyroptosis, the SARS-CoV-2 infection may potentiate or accelerate pre-existing systemic inflammation of individuals with obesity [63]. There is a strong association between inflammation and auto-inflammatory syndromes, a group of genetically induced rheumatic disorders characterized by recurrent episodes of fever and other systemic manifestations triggered by external infections [64] Studies suggest autoinflammation contributes to a number of multifactorial rheumatic diseases, including Behçet's syndrome, seronegative arthritis, and Still's disease [29,65].

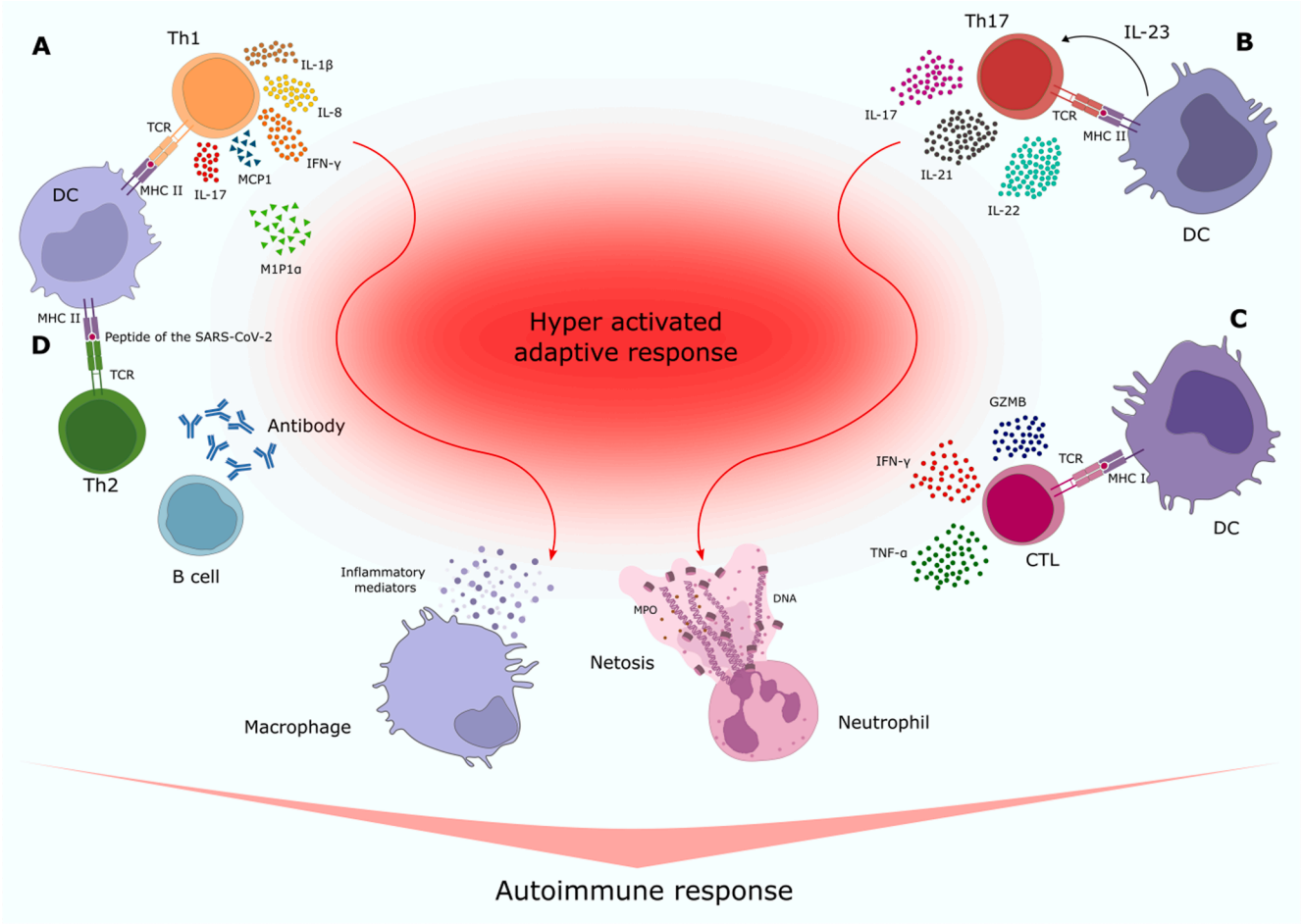

Fig. 2. SARS COV-2 virus can hyperactivate the various parts of adaptive immune system.
An adaptive immune response can follow either a cellular or humoral pathway depending on the antigenic nature (intracellular versus extracellular), however, a disturbed and over-activated immune response may be counterproductive, causing autoimmune response. **A.** Th1 recognizes the peptides of SARS COV-2 and produces inflammatory cytokines, including MCP1, IFNλ, IL1B, IL8, andIL17.Also, Th1 produce large amounts of interferon IFNλ, which activates macrophages, resulting in delayed hypersensitivity. **B.** The Th17 subset responds to SARS COV-2 by producing cytokines, such as IL-17A, IL-17F, IL-21, and IL-22 and recruited neutrophils by T helper 17 cell can lead to autoimmunity reactions by excessive neutrophil extracellular trap formation **C.** As a result of digestion of intracellular antigens, epitopes are usually delivered to CD8 + T lymphocytes, which ultimately act by way of a direct cytotoxic mechanism and produce inflammatory products such as Granzyme B, IFNλ, and TNF-alpha. **D.** Th2 lymphocytes cooperate with B cells in supporting the final maturation in plasma cells and the secretion of specific antiviral antibodies.

4.3. Neutrophil extracellular traps (NETs)

Increased neutrophil counts have been described as an indicator of severe respiratory symptoms in COVID-19 [66]. Among effector mechanisms of neutrophils in inflammatory diseases, neutrophil-derived extracellular traps (NETs) are some of the most important. NETs are networks of extracellular fibers composed of DNA containing histones and granulederived enzymes, such as myeloperoxidase (MPO) and elastase. The process of NET formation by neutrophils, called NETosis, has been widely studied. In general, the process starts with neutrophil activation by pattern recognition receptors or chemokines, followed by ROS production and calcium mobilization, which leads to the activation of protein arginine deiminase 4 (PAD-4), an intracellular enzyme involved in the deamination of arginine residues on histones [67].

Based on studies the concentration of NETs increases in the plasma, tracheal aspirate, and lung tissue specimens of autopsies from COVID-19 patients. Indeed, inflammatory processes are accelerated by NETs when they release a range of active molecules like danger associated molecular patterns (DAMPs), histones, and enzymes that induce further inflammatory responses in the extracellular space. Cell-free DNA, myeloperoxidase-DNA (MPO-DNA), and citrullinated histone H3 (Cit-H3) are NETosis markers, however; Myeloperoxidase-DNA is the most specific marker of NETosis [68–71]. It is important to note that both cell-free DNA and MPO-DNA were higher in hospitalized patients receiving mechanical ventilation as compared with hospitalized patients breathing room air Furthermore, Yu Zuo and colleagues found that circulating neutrophils are infected with SARS-CoV-2 and release high levels of NETs [68].

Indeed, as a consequence of the SARS-CoV-2, healthy neutrophils are capable of releasing NETs, which is mediated by the ACE2–serine protease axis, virus replication, and PAD-4 signaling. Finally, NETs released by SARS-CoV-2– activated neutrophils promote lung epithelial apoptosis. Novel cellular and molecular mechanisms involved in the production of NETs by SARS-CoV-2 infection as well as their possible detrimental role in the pathophysiology of COVID-19 are described here [72] NETs may, therefore, serve as an additional source of auto-antigens against which autoantibodies may be directed by a wide range of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), psoriasis, and gout [73,74] (Figure 1.C). The over-production of NET by CVID-19 can lead to autoimmune diseases in genetically predisposed people. Therefore, the

inhibition of NET release or actions could represent a potential therapeutic target for COVID-19 [75].

4.4. The complement system

The complement system is one of the earliest immune responses to infection,which takes part in the antiviral response through several mechanisms: opsonizing viruses and virus-infected cells (including lysing them), inducing an antiviral immunoinflammatory state, and boosting virus-specific immune responses [76,77]. Pathogens induce an inflammatory response and complement activation at the site of infection in early infection. Depending on the severity of the initial injury and the length of exposure, the complement cascade could be activated excessively or underregulated, leading to additional damage to tissues and cells. SARS-CoV-2 infection activates complement cascade in a similar manner. The glycoprotein S of SARS-CoV can bind to mannose binding lectin and trigger the complement cascade, resulting either in a direct (cytolysis of infected cells) or indirect (immune complex-mediated) viral clearance [78]. Disseminated thrombotic phenomenon, cytokine release syndrome, and the overactive complement system are among the pathological mechanisms that contribute to the worsening of critical conditions of patients requiring intensive care [79,80].

In a histological examination of patients with COVID-19, Magro C and colleagues found spike glycoproteins along with C4d and C5b-9 in the interalveolar septa and cutaneous microvasculature of patients with SARS-CoV-2 [81] as well as, according to a recent preprint study, the highly pathogenic coronavirus N protein aggregated the lung injury caused by SARS-CoV-2 by binding to mannan-binding lectin-associated protease (MASP-2), a serine protease that directly activates the complement cascade [82]. Since SARS-CoV-2 pathogenesis and severity is strongly influenced by complement activation and an overactive complement system may lead to adverse consequences, including fibrosis and inflammation in the musculoskeletal system [78] (Figure 1.D). Dysregulation of the complement system can generate an imbalance between host defense and inflammatory response that leads to autoimmunity. For instance, as a hallmark of SLE, the complement system cascade is hyperactive triggered by autoantibodies and immune complexes through the classical pathway [83,84].

5. The role of adaptive immunity in triggering an autoimmune response in SARS-CoV-2 infections

A functional adaptive immunity is essential for the ultimate clearance of viral infections and for preventing re-infections. Based on the nature of the antigen (intracellular vs extracellular), the adaptive immune response can take a cellular or humoral approach, with T and B lymphocytes leading the way in each case.

5.1. Cellular immunity

Dendritic cells act as connectors between the innate and adaptive immune system. A number of epitopes are present on SARS-CoV-2 envelope proteins, including S, E and M, which can trigger an adaptive immune response once dendritic cells recognize them. Each component of adaptive immunity plays a different role in controlling viral infections, so CD4+ and CD8+ T cells may play different roles [85]. The fact that T lymphocytes can initiate a cytokine storm, which can affect the outcome of COVID-19 patients, should not be overlooked.

In fact, CD4+ T cell responses to SARS-CoV-2 are more prominent than CD8+ T cell responses [86]. One study showed that, patients with severe disease had a lower proportion of IFNγ -producing type 1 helper (Th1) cells [83]; however, type 1 helper T cells (Th1) are capable of producing large amounts of interferon (IFN)γ and activating macrophages, causing delayed hypersensitivity reactions [84] (Figure 2,A). Study results show that patients with severe COVID-19 disease have a complex and overexuberant inflammatory response. ICU patients with COVID- 19 had higher plasma levels of IL1, IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα compared to non-ICU patients with COVID-19. COVID-19 patients were noted to have high amounts of IL1B, IFNγ, IP10 and MCP1 which were leading to activation of *T*-helper-1 (Th1) responses and the resulting cytokine storm was associated with disease severity [83]. In addition, increasing evidence suggests that Th17 cells play an important role in the pathogenesis of COVID-19, not only by activating cytokine cascade but also by inducing Th2 responses, inhibiting Th1 differentiation and suppressing Treg cells. Also, recruited neutrophils by T helper 17 cells (Th17) can lead to autoimmunity reactions [86] (Figure 2,B). COVID-19 lung specimens from patients with increased levels of serum IL-17, IFNγ and multinucleated giant cells are indicative of an activated Th1 and Th17 response [87].

One study evaluated the interplay between Th1 and type 2 helper (Th2) cells in covid-19 patients. They demonstrated for the first time that Th2/Th1 cytokine imbalance in the airway is associated with major COVID-19 risk factors such as age, sex, high ACE2 expression phenotype, and smoking. Based on this study there is also a possible association between worse outcomes and higher Th17 in all patients [85]. The immune system is regulated by cytokines, and inflammatory cytokines cause a deregulation of the immune system and immunopathology. It is possible for people with COVID-19 to develop autoimmune diseases as a result of the cytokine storm syndrome Indeed, Infection with SARS-CoV-2 may result in cytokine storms due to an inadequate immune response to the virus [87]. Furthermore, Blanco-Melo and colleagues demonstrate that infected cells are incapable of producing interferons, which are key mediators of a proper host response against viral infections. They also produce high levels of neutrophil- and macrophage-recruiting chemokines [88]. According to Jiadi Lv et al., innate immune systems may not be able to effectively clear infected cells in the first phase of infection, which could favor virus replication. SARS-CoV-2 survives and replicates inside macrophages [89]. The immune system would regain the ability to fight the virus in a second phase, but since it had been able to replicate undisturbed, an exaggerated reaction of adaptive immune system would result. Moreover, renin-angiotensin-aldosterone system (RAAS), the main receptor used by SARS-CoV-2 to enter human cells can mediate pro-inflammatory, prothrombotic, and profibrotic effects [90,91].

5.2. Humoral immunity

Th2 lymphocytes are involved in the final maturation of plasma cells as well as the release of specific antiviral antibodies that may belong to different isotypic classes (IgM, IgG, IgA). Furthermore, follicular dendritic cells can stimulate B cells in a MHC-independent manner by causing their B cell receptors (BCR) to cross-link in response to multimerized antigens [92]. (Figure 2,D)

There is evidence that the SARS-CoV-2 virus has a critical and pivotal effect on human immunity, and its capability to trigger autoimmune diseases in genetically predisposed individuals, based on the reported inflammatory and autoimmune symptoms, the presence of circulating autoantibodies, and the diagnosis of defined autoimmune diseases in a subgroup of SARS-CoV-2-infected patients [93–96].

5.2.1. Autoantibodies in SARS-CoV-2-infected patients

Researches were conducted to examine the presence of antinuclear antibodies in COVID 19 patients. According to them, ANA-positive patients have a worse prognosis than the negative ones with regards to COVID-19 disease, but a number of limitations prevent conclusions from being drawn, including the small number of patients studied, the different methods for autoantibodies detection, and the genetic heterogeneity of the patients involved. These findings strongly suggest an autoimmune response in these patients [97,98].

Researchers have studied the antiphospholipid (aPL) profile in critically ill COVID-19 patients and found that Intensively ill COVID-19 patients have profound hypercoagulability, leading to complicated venous thrombosis [99,100]. Some studies, however, have claimed that

Table 2
A list of autoantibodies associated with COVID-19 infection.

Circulating autoantibodies reported in COVID-19 patients	Reference
Anti-nuclear antibodies (ANA)	[98,103,104]
LAC	[105,106107,108]
Anti-β2 GPI/Anti-cardiolipin	
Anti-MDA5 antibodies	[109]
Anti RBC antibodies (direct anti globulin)	[97]
Anti-IFN antibodies	[110]
Antiphosphatidylserine IgM/IgG	[102]
Antiannexin V IgM/IgG	[111]
IgG/IgM anti-prothrombin	
Anti-GD1b antibodies	[109]
anti-Caspr2 autoantibodies	
Anti-heparin PF4 complex antibody	
Anti-AT1 antibody/Anti-ACE-2 antibody[1]	[96,113]

[1]Angiotensin type-1 receptors (AA-AT1) and autoantibodies against ACE2 (AA-ACE2).

Table 3
Case reports of the most prevalent autoimmune conditions associated with COVID-19.

Autoimmune disease	Country	Number of patients	Reference
SLE	Iran	1/M	[115]
	Morocco	1/F	[119]
	Japan	1/F	[123]
	Mexico	1/M	[116]
	USA	1/F	[124]
	USA	1/F	[125]
	USA	1/M	[126]
	Italy	1/F	[127]
	USA	1/F	[128]
	Saudi Arabia	1/F	[129]
Guillain-Barre syndrome	Italy	2/M	[130]
	Iran	1/M	[131]
	Iran	1/M	[121]
		1/F	
	Iran	1/M	[132]
	France	1/M	[133]
	Canada	1/M	[134]
	Switzerland	1/M	[135]
	Spain	1/F	[136]
	India	1/M	[137]
	Brazil	1/M	[138]
Autoimmune thyroid disease	Spain	2/F	[139]
	China	28 patients	[140]
	USA	1/F	
Immune thrombocytopenic purpura	UK	2/F	[141142143]
	The	1/M	
	Netherlands	2/M	
	France	1/F	
		7/F	
		7/M	
	Turkey	2/F	[144]
	Portugal	2/F	[145]
	United States	2/M	[146]

there is no correlation between aPL positivity and disease outcomes such as thrombosis, invasive ventilation, and mortality. It remains to be determined the clinical and pathological importance of aPL in COVID-19 [101,102] (Table 2).

6. Reports of the most prevalent autoimmune conditions associated with COVID-19

There have been a growing number of reports describing autoimmune reactions associated with COVID-19 infection. The time between symptoms of viral illness and onset of autoimmune symptoms ranged from 2 days to 33 day [114]. For instance, the first case of systematic lupus erythematosus (SLE) following covid-19 infection was reported by Batool Zamani in Iran. The patient was a 39-year-old Iranian/Persian man who had been infected with SARS-CoV-2 two months ago. He complained of fever, scaling on the palms of his hands and feet, lower extremity edema, and ankle swelling and patient had proteinuria and was positive for SLE laboratory tests [115]. It is challenging to diagnose SLE in patients who have been infected by SARS-CoV-2. We know from the present series that severe thrombocytopenia, serositis, and kidney damage are clinical indicators that could aid in differential diagnosis. In the presence of such findings, immunological markers should be determined to confirm or rule out the presence of SLE. SLE activity should be diagnosed promptly so that specific treatment can be initiated without delay [116].

A COVID-19 infection can produce neurological symptoms by affecting the central nervous system (CNS) (headache, dizziness, consciousness disorder, acute brain disease, seizures, and ataxia) [117], the peripheral nervous system (PNS) (anosmia, ageusia, visual impairment, nerve pain), and the skeletal muscles [118]. The acute polyneuropathy characterized by SARS-CoV-2 has been documented in a few case reports [119]. Studies have shown that the days between COVID-19 symptoms and GBS onset can vary between 3 and 30 days in different cases. There have been 73 cases of Guillain-Barre following covid-19 reported throughout the world so far [120]. One of the most curious reports regarding GBS following COVI-19 infection was released by Sepideh Paybast in Iran, which revealed the familial occurrence of GBS following COVID-19 infection in one father and his daughter [121].

There are several studies, which documented the occurrence of Graves' thyrotoxicosis following mild symptomatic COVID-19. These reports may align with the theory of a viral link in the development of autoimmune thyroid disease in those with genetic predisposition. An overview of the recent reports regarding the most prevalent autoimmune conditions associated COVID-19 is provided in Table 3.

7. The effect of some autoimmune disease drugs on the clinical course of patients with COVID-19

COVID-19 and autoimmune diseases share a common pathogenesis, making autoimmune drugs a possible treatment option. In several studies, drugs commonly used to treat autoimmunity were found to be effective in covid-19 patients as well. For example, in Th17 cell differentiation, STAT3 is activated by IL-6 and IL-23 through JAK2 and JAK1. SLE and COVID-19 patients' clinical conditions can be improved by regulating JAK2, which is a bridge to differentiation and function of Th17 cells [147]. Chloroquine (CQ) can interfere with the glycosylation of the ACE2 by binding to the virus and inhibiting respiratory syndrome in COVID-19 patients. Rheumatoid arthritis patients may benefit from

Table 4
Some of the most effective autoimmune diseases drugs on the clinical course of COVID-19 patients.

Autoimmune disease	Medicine	Drug function	Possible response in COVID-19 patients	Reference
Systemic lupus erythematosus	Fedratinib	JAK2 dedicated inhibitor	Reduced risk of cytokine storms	[152]
	Chloroquine	Connecting to DNA and interfering with protein production	Interference with glycosylation of the ACE2 and reduced risk of cytokine storms	[153]
Rheumatoid Arthritis	Baricitinib	JAK1/2 inhibitor	Control of exaggerated inflammatory responses	[148]
Multiple sclerosis	Tocilizumab	IL-6 receptor blocker	Reduced risk of cytokine storms	[149]

Baricitinib, a reversible oral inhibitor of the Janus kinases JAK1 and JAK2.This drug interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology. It may also inhibit angiotensin-converting-enzyme-2 upregulation by targeting host factors that viruses rely on for entry into cells. However, during acute viral infections, Baricitinib's immunosuppressive effects may delay viral clearance and increase vulnerability to secondary infections [148]. Another effective drug, which is common between COVID-19 and Multiple sclerosis is Tocilizumab, which is a IL-6 receptor blocker and can reduce cytokine storm and hyperactivation of immune system.Infact, the blocking of interleukin-6 would benefit COVID-19 patients with enhanced inflammation, as demonstrated by increased levels of certain inflammatory biomarkers [149]. In patients with COVID-19, immunosuppressive drugs are either beneficial or detrimental. In the initial phase of COVID-19, immunosuppressive drugs may be harmful. In this phase, the host immune response is necessary to inhibit viral replication. However, immunosuppressive drugs might have a beneficial effect in the later, more severe phase of COVID-19 due to cytokine storm. In fact, using immunosuppression to treat hyperinflammation in COVID-19 is a double-edged sword [150]. This table (Table 4) presents some effective autoimmune disease drugs on the clinical course of COVID-19 patients.

A treatment approach based on immune cells is also available for both COVID-19 and autoimmune diseases. The adoptive immune cell therapy to recover cell-mediated immunocompetence, represents a promising treatment for patients with COVID-19. It is imperative to use an effective treatment strategy such as immuno-cell therapy to modulate the immune system's over-activation and increase its ability to kill the COVID-19 virus. These approaches are particularly focused on targeting inflammatory processes, and raising the effective immune response against the SARS-CoV-2 by using adaptive immune system cells such as NK, Treg,specific T cell, DC, Monocyte [151].

8. Conclusion

SARS-CoV-2, like many viruses like EBV, CMV, HIV, and HTLV-1, is capable of causing autoimmunity. Several mechanisms are thought to be capable of contributing to the development of autoimmunity in COVID-19, including SARS-CoV-2′s ability to perturb the immune system, excessive NETosis formation with neutrophil-associated cytokine responses, and the molecular resemblance between host components and the virus [154]. There have been several reports of autoimmune manifestations in patients with SARS-CoV-2. This suggests that COVID-19 is capable of causing autoimmune diseases in vulnerable patients. After contracting CVID-19, physicians must monitor susceptible patients for autoimmune symptoms. Since there are no specific medicines for COVID-19, studies suggest autoimmune drugs as a potential treatment because autoimmune diseases and COVID-19 share a common pathogenesis.However, vaccination is the best remedy for dealing with this pandemic, but concerns have been raised about triggering autoimmune diseases like previous virus vaccinations [155]. How likely is it that the Covid-19 vaccines will cause autoimmune disease?

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.

Data availability

No data was used for the research described in the article.

References

[1] J. Tu, et al., The possible effect of B-cell epitopes of Epstein-Barr virus early antigen, membrane antigen, latent membrane protein-1, and -2A on systemic lupus erythematosus, Front. Immunol. 9 (2018) 187.
[2] M. EJ, et al., Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis, Nat. Med. 11(3) (2005) 335–339.
[3] Q. Pan, et al., Current mechanistic insights into the role of infection in systemic lupus erythematosus, Biomed. Pharmacother. 117 (2019), 109122.
[4] S. Levet, et al., Human Endogenous Retroviruses and Type 1 Diabetes, Curr. Diab. Rep. 19 (12) (2019) 141.
[5] T. Rodriguez-Calvo, Enteroviral Infections as a Trigger for Type 1 Diabetes, Curr. Diab. Rep. 18 (11) (2018) 106.
[6] CY, P., et al., Association of cytomegalovirus infection with autoimmune type 1 diabetes, Lancet 332(8601) (1988) 1-4.
[7] AM, E. and M. SD, The role of infections in autoimmune disease, Clin. Exp. Immunol. 155(1) (2009) 1–15.
[8] U. Christen, Pathogen infection and autoimmune disease, Clin. Exp. Immunol. 195 (1) (2019) 10–14.
[9] G.R. Gallagher, et al., Viral infection of engrafted human islets leads to diabetes, Diabetes 64 (4) (2015) 1358–1369.
[10] R. Varela-Calvino, G. Sgarbi, L.R. Wedderburn, T cell activation by coxsackievirus B4 antigens in type 1 diabetes mellitus: evidence for selective TCR Vbeta usage without superantigenic activity, J. Immunol. 167 (6) (2001) 3513–3520.
[11] B. Conrad, et al., A human endogenous retroviral superantigen as candidate autoimmune gene in type I diabetes, Cell 90 (2) (1997) 303–313.
[12] L.C. Stene, M. Rewers, Immunology in the clinic review series; focus on type 1 diabetes and viruses: the enterovirus link to type 1 diabetes: critical review of human studies, Clin. Exp. Immunol. 168 (1) (2012) 12–23.
[13] E. Treppo, et al., Rheumatologic manifestations of Hepatitis C Virus, Minerva Med. 112 (2) (2021) 201–214.
[14] U. Stölzel, et al., Autoimmunity and HCV Infection in Porphyria Cutanea Tarda: A Controlled Study, Cell. Mol. Biol. 48 (1) (2002) 43–47.
[15] J, C., Z. H, and C. P, Correlation between systemic lupus erythematosus and cytomegalovirus infection detected by different methods, Clin. Rheumatol. 34(4) (2015) 691–698.
[16] S. Talib, et al., Dengue fever triggering systemic lupus erythematosus and lupus nephritis: a case report, Int. Med. Case Rep. J. 6 (2013) 71–75.
[17] S, A., et al., Parvovirus B19 infection and systemic lupus erythematosus: activation of an aberrant pathway? Eur. J. Int. Med. 19(5) (2008) 314–318.
[18] J. Cui, et al., Anti-Epstein-Barr virus antibodies in Beijing during 2013–2017: What we have found in the different patients, PLoS ONE 13 (3) (2018) e0193171.
[19] D, C., et al., Association of clinical and serological parameters of systemic lupus erythematosus patients with Epstein-Barr virus antibody profile, J. Med. Virol. 90 (3) (2018) 559–563.
[20] M.R.d. Costa, et al., Prevalence and genetic diversity of torque teno virus in patients with systemic lupus erythematosus in a reference service in Mato Grosso do Sul, Rev. Bras. Reumatol. 25(1) (2012) 49–54.
[21] B. Serafini, et al., Epstein-Barr Virus-Specific CD8 T Cells Selectively Infiltrate the Brain in Multiple Sclerosis and Interact Locally with Virus-Infected Cells: Clue for a Virus-Driven Immunopathological Mechanism, J. Virol. 93 (24) (2019) e00980–e01019.
[22] F. Läderach, C. Münz, Epstein Barr Virus Exploits Genetic Susceptibility to Increase Multiple Sclerosis Risk, Microorganisms 9 (11) (2021).
[23] G, W., TuckerR, and A. Paskauskas, The MSMV hypothesis: Measles virus and multiple sclerosis, etiology and treatment, Med. Hypotheses 71(5) (2008) 682–689.
[24] C. Otto, J. Hofmann, K. Ruprecht, Antibody producing B lineage cells invade the central nervous system predominantly at the time of and triggered by acute Epstein-Barr virus infection: A hypothesis on the origin of intrathecal immunoglobulin synthesis in multiple sclerosis, Med. Hypotheses 91 (2016) 109–113.
[25] J. Sotelo, et al., The participation of varicella zoster virus in relapses of multiple sclerosis, Clin. Neurol. Neurosurg. 119 (2014) 44–48.
[26] F. Caso, et al., Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun. Rev. 19 (5) (2020), 102524.
[27] S. Najafi, E. Rajaei, R. Moallemian, The potential similarities of COVID-19 and autoimmune disease pathogenesis and therapeutic options: new insights approach, 39(11) (2020) 3223–3235.
[28] Y. Liu, A.H. Sawalha, Q. Lu, COVID-19 and autoimmune diseases, Curr. Opin. Rheumatol. 33 (2) (2021) 155–162.
[29] R. Talotta, E. Robertson, Autoimmunity as the comet tail of COVID-19 pandemic, 8(17) (2020) 3621–3644.
[30] S, L., et al., Human Endogenous Retroviruses and Type 1 Diabetes, Curr. Diab. Rep, 19(12) (2019) p. 141.
[31] Rodriguez-Calvo1, T., Enteroviral Infections as a Trigger for Type 1 Diabetes, Curr. Diab. Rep. 18(11) (2018) p. 106.
[32] J, C., et al., Anti-Epstein–Barr virus antibodies in Beijing during 2013–2017: What we have found in the different patients, PLoS ONE 13 (2018) p. e0193171.
[33] F. Läderach, C.M. 1, Epstein Barr Virus Exploits Genetic Susceptibility to Increase Multiple Sclerosis Risk, Microorganisms. Microorganisms 9(11): p. 2191.
[34] B.F. Koch, SARS-CoV-2 and human retroelements: a case for molecular mimicry? BMC Genom Data 23 (1) (2022) 27.
[35] G, L. and F. A, Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons, Autoimmun. Rev. 19(7) (2020) p. 102556.

[36] Z. Balogi, et al., Hsp70 interactions with membrane lipids regulate cellular functions in health and disease, Prog. Lipid Res. 74 (2019) 18–30.
[37] G, L., Epitopes for a 2019-nCoV vaccine, Cell Mol. Immunol. 17(5) (2020) 539–540.
[38] B.F. Koch, SARS-CoV-2 and human retroelements: a case for molecular mimicry? BMC Genomic Data 23 (1) (2022) 1–9.
[39] F, C., Is COVID-19 a proteiform disease inducing also molecular mimicry phenomena? Cell Stress Chaperones 25(3) (2020) 381–382.
[40] Z, B., et al., Hsp70 interactions with membrane lipids regulate cellular functions in health and disease, Prog. Lipid Res. 74 (2019) 18–30.
[41] C, C.B., et al., Hsp60 Post-translational Modifications: Functional and Pathological Consequences, Front. Mol. Biosci. 7 (2020) p. 95.
[42] K. Mandal, M. Jahangiri, Q. Xu, Autoimmunity to heat shock proteins in atherosclerosis, Autoimmun. Rev. 3 (2) (2004) 31–37.
[43] F, C., et al., Chlamydia trachomatis infection and anti-Hsp60 immunity: the two sides of the coin, PLoS Pathog. 5(8) (2009) p. e1000552.
[44] A.M. Gammazza, et al., Human molecular chaperones share with SARS-CoV-2 antigenic epitopes potentially capable of eliciting autoimmunity against endothelial cells: possible role of molecular mimicry in COVID-19, 25(2) (2020) 737–741.
[45] Z. Xu, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, 8(4) (2020) 420–422.
[46] H.N. Eisen, A.K. Chakraborty, Evolving concepts of specificity in immune reactions, Proc. Natl. Acad. Sci. U S A 107 (52) (2010) 22373–22380.
[47] S.W. Brubaker, et al., Innate immune pattern recognition: a cell biological perspective, Annu. Rev. Immunol. 33 (2015) 257–290.
[48] F, C., et al., The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system, Cytokine Growth Factor Rev. 53 (2020) 25–32.
[49] JB, M. and J. CH, Cytokine release syndrome in severe COVID-19, Science 368 (6490) (2020) 473–474.
[50] R. Medzhitov, Recognition of microorganisms and activation of the immune response, Nature 449 (7164) (2007) 819–826.
[51] HN, E. and C. AK, Evolving concepts of specificity in immune reactions, Proc. Natl. Acad. Sci. U S A 107(52) (2010) 22373–22380.
[52] SW, B., et al., Innate immune pattern recognition: a cell biological perspective, Annu. Rev. Immunol. 33 (2015) 257–290.
[53] S. Khanmohammadi, N. Rezaei, Role of Toll-like receptors in the pathogenesis of COVID-19, J. Med. Virol. 93 (5) (2021) 2735–2739.
[54] P, C., R. G, and C. A, Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies, J. Biol. Regul. Homeost. Agents 34(2) (2020) 327–331.
[55] W. CE, et al., Network analysis of associations between serum interferon-α activity, autoantibodies, and clinical features in systemic lupus erythematosus, Arthritis Rheum. 63(4) (2011) 1044–1053.
[56] L, R., E. ML, The interferon signature in autoimmune diseases, Curr. Opin. Rheumatol. 25(2) (2013) 248–253.
[57] P. Conti, et al., Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies, J. Biol. Regul. Homeost. Agents 34 (2) (2020) 327–331.
[58] C. IY, I. T, Response of host inflammasomes to viral infection, Trends Microbiol. 23(1) (2015) 55–63.
[59] S. Cicco, et al., Neutrophil Extracellular Traps (NETs) and Damage-Associated Molecular Patterns (DAMPs): Two Potential Targets for COVID-19 Treatment, Mediators Inflamm. 2020 (2020) 7527953.
[60] S. Khadke, et al., Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: a review of the phases of illness and therapeutic agents, Virol. J. 17 (1) (2020) 154.
[61] G. Lopalco, et al., Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives, Mediators Inflamm. 2015 (2015), 194864.
[62] P, C., et al., Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies, J. Biol. Regul. Homeost. Agents 34(2) (2020) 327–331.
[63] I. Bertocchi, et al., The hidden role of NLRP3 inflammasome in obesity-related COVID-19 exacerbations: Lessons for drug repurposing, Br. J. Pharmacol. 177 (21) (2020) 4921–4930.
[64] L, B., et al., The inflammasomes and autoinflammatory syndromes, Annu. Rev. Pathol. 10 (2015) 395–424.
[65] G, L., et al., Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives, Mediators Inflamm. 2015(194864) (2015).
[66] L. Borges, et al., COVID-19 and Neutrophils: The Relationship between Hyperinflammation and Neutrophil Extracellular Traps, Mediators Inflamm. 2020 (8829674) (2020).
[67] C. Radermecker, et al., Neutrophil extracellular traps infiltrate the lung airway, interstitial, and vascular compartments in severe COVID-19, J. Exp. Med. 217 (12) (2020).
[68] Y. Zuo, et al., Neutrophil extracellular traps in COVID-19, JCI Insight 5 (11) (2020) e138999.
[69] N. Kinnare, et al., Neutrophil Extracellular Trap Formation Potential Correlates with Lung Disease Severity in COVID-19 Patients, Inflammation (2021) 1–12.
[70] F.P. Veras, et al., SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology, J. Exp. Med. 217 (12) (2020).
[71] C. Radermecker, N. Detrembleur, J. Guiot, Neutrophil extracellular traps infiltrate the lung airway, interstitial, and vascular compartments in severe COVID-19, J. Exp. Med. 217 (12) (2020) e20201012.
[72] F.P. Veras, et al., SARS-CoV-2–triggered neutrophil extracellular traps mediate COVID-19 pathology, 217(12) (2020).
[73] K.H. Lee, et al., Neutrophil extracellular traps (NETs) in autoimmune diseases: A comprehensive review, Autoimmun. Rev. 16 (11) (2017) 1160–1173.
[74] E. Fousert, R. Toes, J. Desai, Neutrophil Extracellular Traps (NETs) Take the Central Stage in Driving Autoimmune Responses, Cells 9 (4) (2020) 915.
[75] E.A. Middleton, et al., Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome, Blood 136 (10) (2020) 1169–1179.
[76] Nasir A, C.-A.G., A phylogenomic data-driven exploration of viral origins and evolution, Sci. Adv. 1(8) (2015) p. e1500527.
[77] MG, N., S. A, and R. N, SARS-CoV-2-A Tough Opponent for the Immune System, Arch Med. Res. 51(6) (2020) 589–592.
[78] KA, S. and M. TE, Complement and viral pathogenesis, Virology 411(2) (2011) 362–373.
[79] M, N. and R. G, Atypical hemolytic uremic syndrome associated with a factor B genetic variant and fluid-phase complement activation: an exception to the rule?. Kidney Int. 98(5) (2020) 1084-1087.
[80] X. Wang, K.K. Sahu, J. Cerny, Coagulopathy, endothelial dysfunction, thrombotic microangiopathy and complement activation: potential role of complement system inhibition in COVID-19, 51(3) (2021) 657–662.
[81] C, M., et al., Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases, Transl. Res. 220 (2020) 1–13.
[82] A. Grifoni, et al., Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals, Cell 181(7) (2020) p. 1489-1501.e15.
[83] G. Chen, et al., Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (5) (2020) 2620–2629.
[84] T. Mosmann, R. Coffman, TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties, Annu. Rev. Immunol. 7 (1) (1989) 145–173.
[85] A. Sette, S. Crotty, Adaptive immunity to SARS-CoV-2 and COVID-19, Cell 184 (4) (2021) 861–880.
[86] A. Grifoni, et al., Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals, Cell 181(7) (2020) p. 1489-1501. e15.
[87] A. Maiese, et al., Thromboinflammatory response in SARS-CoV-2 sepsis, Med. Leg. J. 88 (2) (2020) 78–80.
[88] D. Blanco-Melo, et al., Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181(5) (2020) p. 1036-1045. e9.
[89] J. Lv, et al., Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages, Cell Discovery 7 (1) (2021) 1–12.
[90] M. Gheblawi, et al., Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2, 126 (2020) 1456–1474.
[91] P. Domingo, et al., The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19), EBioMedicine 58 (2020), 102887.
[92] ME, E.S., et al., Activation of B cells by antigens on follicular dendritic cells, Trends Immunol. 31(6) (2010) 205–211.
[93] H. Fujii, et al., High levels of anti-SSA/Ro antibodies in COVID-19 patients with severe respiratory failure: a case-based review: High levels of anti-SSA/Ro antibodies in COVID-19, Clin. Rheumatol. 39 (11) (2020) 3171–3175.
[94] Y. Zhang, et al., Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients, J. Thromb. Thrombolysis 50 (3) (2020) 580–586.
[95] P. Bastard, et al., Autoantibodies against type I IFNs in patients with life-threatening COVID-19, Science 370 (6515) (2020).
[96] A.I. Rodriguez-Perez, et al., Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19, J. Autoimmun. 122 (2021), 102683.
[97] G. Halpert, Y. Shoenfelda, SARS-CoV-2, the autoimmune virus, Autoimmun. Rev. 19 (12) (2020), 102695.
[98] P. Muratori, et al., Antinuclear antibodies in COVID 19, Clin. Transl. Sci. 14 (5) (2021) 1627–1628.
[99] Y, Z., et al., Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients, Thromb Thrombolysis 50(3) (2020) 580–586.
[100] Y. Zhang, et al., Profile of natural anticoagulant, coagulant factor and anti-phospholipid antibody in critically ill COVID-19 patients, 50(3) (2020) 580–586.
[101] L. Bowles, et al., Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19, N. Engl. J. Med. 383 (3) (2020) 288–290.
[102] M. Taha, L. Samavati, Antiphospholipid antibodies in COVID-19: a meta-analysis and systematic review, RMD Open 7 (2) (2021) e001580.
[103] S.H. Chang, D. Minn, Y.K. Kim, Autoantibodies in moderate and critical cases of COVID-19, Clin. Transl. Sci. 14 (5) (2021) 1625–1626.
[104] H, F., et al., High levels of anti-SSA/Ro antibodies in COVID-19 patients with severe respiratory failure: a case-based review: high levels of anti-SSA/Ro antibodies in COVID-19, Clin. Rheumatol. 39(11) (2020) 3171–3175.
[105] I. Harzallah, A. Debliquis, B. Drénou, Lupus anticoagulant is frequent in patients with Covid-19, J. Thromb. Haemost. 18 (8) (2020) 2064–2065.
[106] C. Gazzaruso, G. Mariani, Lupus anticoagulant and mortality in patients hospitalized for COVID-19, J. Thromb. Thrombolysis 52 (1) (2021) 85–91.

[107] Y., X.Z. and Z. S, Brief report: anti-phospholipid antibodies in critically-ill patients with coronavirus disease 2019 COVID-19, Arthritis Rheum. 72(12) (2020) 1998–2004.
[108] G, V., et al., Autoantibodies related to systemic autoimmune rheumatic diseases in severely-ill patients with COVID-19, Ann. Rheum. Dis. 79(12) (2020) 1661–1663.
[109] A. Guilmot, et al., Immune-mediated neurological syndromes in SARS-CoV-2-infected patients, J. Neurol. 268 (3) (2021) 751–757.
[110] D. Dragonetti, G. Guarini, M. Pizzuti, Detection of anti-heparin-PF4 complex antibodies in COVID-19 patients on heparin therapy, Blood Transfus 18 (4) (2020) 328.
[111] A. Cristiano, V. Fortunati, F. Cherubini, Anti-phospholipids antibodies and immune complexes in COVID-19 patients: a putative role in disease course for anti-annexin-V antibodies, Clin. Rheumatol. 40 (7) (2021) 2939–2945.
[113] A.I. Rodriguez-Perez, et al., Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19, J. Autoimmun. 122 (102683) (2021).
[114] M.A. Saad, et al., COVID-19 and Autoimmune Diseases: A Systematic Review of Reported Cases, Bentham Sci. 17 (2) (2021).
[115] B. Zamani, S.-M.-M. Taba, M. Shayestehpour, Systemic lupus erythematosus manifestation following COVID-19: a case report, J. Med. Case Rep. 15 (1) (2021) 29.
[116] A.E. Gracia-Ramos, M.Á. Saavedra-Salinas, Can the SARS-CoV-2 infection trigger systemic lupus erythematosus? A case-based review, Rheumatol. Int. 41 (4) (2021) 799–809.
[117] D, W., et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, Jama 323(11) (2020) 1061–1069.
[118] A. Harris, M. Al Mushref, Graves',, Thyrotoxicosis Following SARS-CoV-2 Infection, AACE Clin. Case Rep. 7 (1) (2021) 14–16.
[119] Y. Slimani, et al., Systemic lupus erythematosus and varicella-like rash following COVID-19 in a previously healthy patient, J. Med. Virol. 93 (2) (2021) 1184–1187.
[120] S. Abu-Rumeileh, et al., Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases, J. Neurol. 1268 (4) (2021) 1133–1170.
[121] S. Paybast, R. Gorji, S. Mavandadi, Guillain-Barré Syndrome as a Neurological Complication of Novel COVID-19 Infection: A Case Report and Review of the Literature, Neurologist. 25 (4) (2020) 101–103.
[123] S. Raghavan, et al., A case of systemic lupus erythematosus flare triggered by severe coronavirus disease 2019, J. Clin. Rheumatol. 26 (6) (2020) 234–235.
[124] A. Kichloo, et al., COVID-19 and Acute Lupus Pneumonitis: Diagnostic and Treatment Dilemma, J. Investig. Med. High Impact Case Rep. 8 (2324709620933438) (2020).
[125] A. Hayden, et al., Severe refractory thrombocytopenia in a woman positive for coronavirus disease 2019 with lupus and antiphospholipid syndrome, Lupus 29 (11) (2020) 1472–1474.
[126] S, R., et al., A Case of Systemic Lupus Erythematosus Flare Triggered by Severe Coronavirus Disease 2019, J. Clin. Rheumatol. 26(6) (2020) 234–235.
[127] R, B., et al., The first case of systemic lupus erythematosus (SLE) triggered by COVID-19 infection, Eur. Rev. Med. Pharmacol. Sci. 24(18) (2020) 9695–9697.
[128] A, H., et al., Severe refractory thrombocytopenia in a woman positive for coronavirus disease 2019 with lupus and antiphospholipid syndrome, Lupus 29 (11) (2020) 1472–1474.
[129] A, A., et al., COVID-19 in a patient with a flare of systemic lupus erythematosus: A rare case-report, Respir. Med. Case Rep. 31 (2020) p. 101252.
[130] Assini A, B.L., Di Maio S, Schirinzi E, Del Sette M. New, clinical manifestation of COVID-19 related Guillain-Barrè syndrome highly responsive to intravenous immunoglobulins: two Italian cases, Neurol Sci. 41(7) (2020) 1657–1658.
[131] Z. Sedaghat, N. Karimi, Guillain Barre syndrome associated with COVID-19 infection: A case report, J. Clin. Neurosci. 76 (2020) 233–235.
[132] M.A. Farzi, et al., Guillain-Barré syndrome in a patient infected with SARS-CoV-2, a case report, J. Neuroimmunol. 346 (577294) (2020).
[133] S, A., B. C, and N.W.T. S, Post SARS-CoV-2 Guillain-Barré syndrome, Clin. Neurophysiol. 131(7) (2020) 1652–1654.
[134] J.L. Chan, H. Ebadi, J.R. Sarna, Guillain-Barré Syndrome with Facial Diplegia Related to SARS-CoV-2 Infection, Can. J. Neurol. Sci. 47 (6) (2020) 852–854.
[135] A. Lampe, et al., Guillain-Barré syndrome and SARS-CoV-2, Neurol. Res. Pract. 2 (1) (2020) 19.
[136] A.E. Molina, et al., Guillain-Barré Syndrome Associated with SARS-CoV-2 infection, Med. Intensiva (Engl. Ed) 44 (8) (2020) 513–514.
[137] J. Finsterer, S.F., R. Ghosh, COVID-19 polyradiculitis in 24 patients without SARS-CoV-2 in the cerebro-spinal fluid, J. Med. Virol. 93(1) (2021) p. 66–68.
[138] C.H.M. Frank, et al., Guillain-Barré Syndrome Associated with SARS-CoV-2 Infection in a Pediatric Patient, J. Trop. Pediatr. 67 (3) (2021).
[139] M, M.S., U. E, and C. A, SARS-COV-2 as a trigger for autoimmune disease: report of two cases of Graves' disease after COVID-19, J. Endocrinol. Invest. 43(10) (2020) 1527–1528.
[140] M, C., Z. W, and X. W, Thyroid function analysis in 50 patients with COVID-19: a retrospective study, Thyroid 31(1) (2021) p. 8–11.
[141] M.Z. Ahmed, et al., Thrombocytopenia as an initial manifestation of COVID-19; case series and literature review, Br. J. Haematol. 189 (6) (2020) 1057–1058.
[142] G, B., M. P, and L. F, COVID-19-associated immune thrombocytopenia, Br. J. Haematol. 190(2) (2020) p. e61-e64.
[143] M, M., M. G, and A. E, Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series. Br. J. Haematol. 190(4) (2020) p. e224-e229.
[144] F.Y. Aydın, V. Demircan, Diagnosis and management of coronavirus disease-associated immune thrombocytopenia: a case series, Rev. Soc. Bras. Med. Trop 54 (2021) p. e0029 2021.
[145] A, P., et al., Immune thrombocytopenic purpura—different presentations in two COVID-19 patients, Cureus 12(10) (2020) p. e11202.
[146] N, G., R. T, S. Yet, SARS-CoV-2 Infection Inducing immune thrombocytopenic purpura: case series, Ochsner J. 21(2) (2021) 187–189.
[147] L.A. Zenewicz, IL-22: there is a gap in our knowledge, Immunohorizons 2 (6) (2018) 198–207.
[148] A.C. Kalil, et al., Baricitinib plus remdesivir for hospitalized adults with Covid-19, N. Engl. J. Med. 384 (9) (2021) 795–807.
[149] N. Broman, et al., Early administration of tocilizumab in hospitalized COVID-19 patients with elevated inflammatory markers; COVIDSTORM—a prospective, randomized, single-centre, open-label study, Clin. Microbiol. Infect. (2022).
[150] A.I. Ritchie, A. Singanayagam, Immunosuppression for hyperinflammation in COVID-19: a double-edged sword, Lancet 395 (10230) (2020) 1111.
[151] M. Zavvar, et al., COVID-19 immunotherapy: Treatment based on the immune cell-mediated approaches, Int. Immunopharmacol. (2022) 108655.
[152] D. Wu, X.O. Yang, TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib, J. Microbiol. Immunol. Infect. 53 (3) (2020) 368–370.
[153] D. Jakhar, I. Kaur, Potential of chloroquine and hydroxychloroquine to treat COVID-19 causes fears of shortages among people with systemic lupus erythematosus, Nat. Med. 26(5) (2020) 632–632.
[154] A. Dotan, et al., The SARS-CoV-2 as an instrumental trigger of autoimmunity, Autoimmun. Rev. 20 (4102792) (2021).
[155] Y. Segal, Y. Shoenfeld, Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction, Cell. Mol. Immunol. 15 (6) (2018) 586–594.