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Review

Long COVID Definition, Symptoms, Risk Factors, Epidemiology and Autoimmunity: A Narrative Review ☆

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ABSTRACT

The virus called SARS-CoV-2 emerged in 2019 and quickly spread worldwide, causing COVID-19. It has greatly impacted on everyday life, healthcare systems, and the global economy. In order to save as many lives as possible, precautions such as social distancing, quarantine, and testing policies were implemented, and effective vaccines were developed. A growing amount of data collected worldwide allowed the characterization of this new disease, which turned out to be more complex than other common respiratory tract infections. An increasing number of convalescents presented with a variety of nonspecific symptoms emerging after the acute infection. This possible new global health problem was identified and labelled as long COVID. Since then, a great effort has been made by clinicians and the scientific community to understand the underlying mechanisms and to develop preventive measures and effective treatment. The role of autoimmunity induced by SARS-CoV-2 infection in the development of long COVID is discussed in this review. We aim to deliver a description of several conditions with an autoimmune background observed in COVID-19 convalescents, including Guillain-Barré syndrome, antiphospholipid syndrome and related thrombosis, and Kawasaki disease highlighting a relationship between SARS-CoV-2 infection and the development of autoimmunity. However, further studies are required to determine its true clinical significance.

Introduction

An increasing number of respiratory tract acute infections caused by a novel coronavirus was observed in Wuhan, China, in November 2019.[1] The pathogen was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease as coronavirus disease 2019 (COVID-19).[2] Due to the rapid spreading of the disease, the World Health Organization (WHO) declared COVID-19 a pandemic in May 2020.[3] According to the WHO report, from the first COVID-19 cases in November 2019 to March 2023, approximately 759 million SARS-CoV-2 infections and 6.9 million deaths due to COVID-19 have been confirmed worldwide. In the same document, the WHO estimated the number of COVID-19-related excess deaths was approximately 14.9 million by the end of 2021, and nearly 337 million years of life were lost in 2020-2021 due to the pandemic.[4] Respiratory symptoms range from asymptomatic or mild coryza to severe pneumonia and damage to alveoli and capillaries caused by hyperinflammation resulting in impaired gas exchange and, in turn, hypoxia, a state called acute respiratory distress syndrome (ARDS). Despite the name of the pathogen indicating respiratory involvement, COVID-19 may impair many other systems and organs, and should be considered a systemic multiorgan disease.[5] Data collected from clinical practice and observation, as well as scientific studies, showed an unquestionable negative impact of SARS-CoV-2 infection on the cardiovascular,[6-8] renal,[9-12] gastrointestinal,[13-16] nervous,[17-20] and skin systems.[21-23] The clinical presentation and severity of COVID-19 symptoms have changed over time, with approximately

Abbreviations: ACE2, angiotensin-converting enzyme 2 receptor; aCL, anticardiolipin antibodies; ADAR1, adenosine deaminase RNA specific 1 enzyme; ADCC, antibody-dependent cell-mediated cytotoxic effect; ADCP, antibody-dependent cellular phagocytosis; AIDP, acute inflammatory demyelinating polyneuropathy; AIH, autoimmune hepatitis; AKI, acute kidney injury; AMAN, acute motor axonal neuropathy; AMSAN, acute motor-sensory and axonal neuropathy; ANA, antinuclear antibodies; AOSD, adult-onset Still's disease; APLAs, antiphospholipid antibodies; APOBEC, apolipoprotein B mRNA editing catalytic polypeptide-like enzyme; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; BMI, body mass index; BNP, brain natriuretic peptide; β2-GPI, anti-β2-glycoprotein I antibodies.

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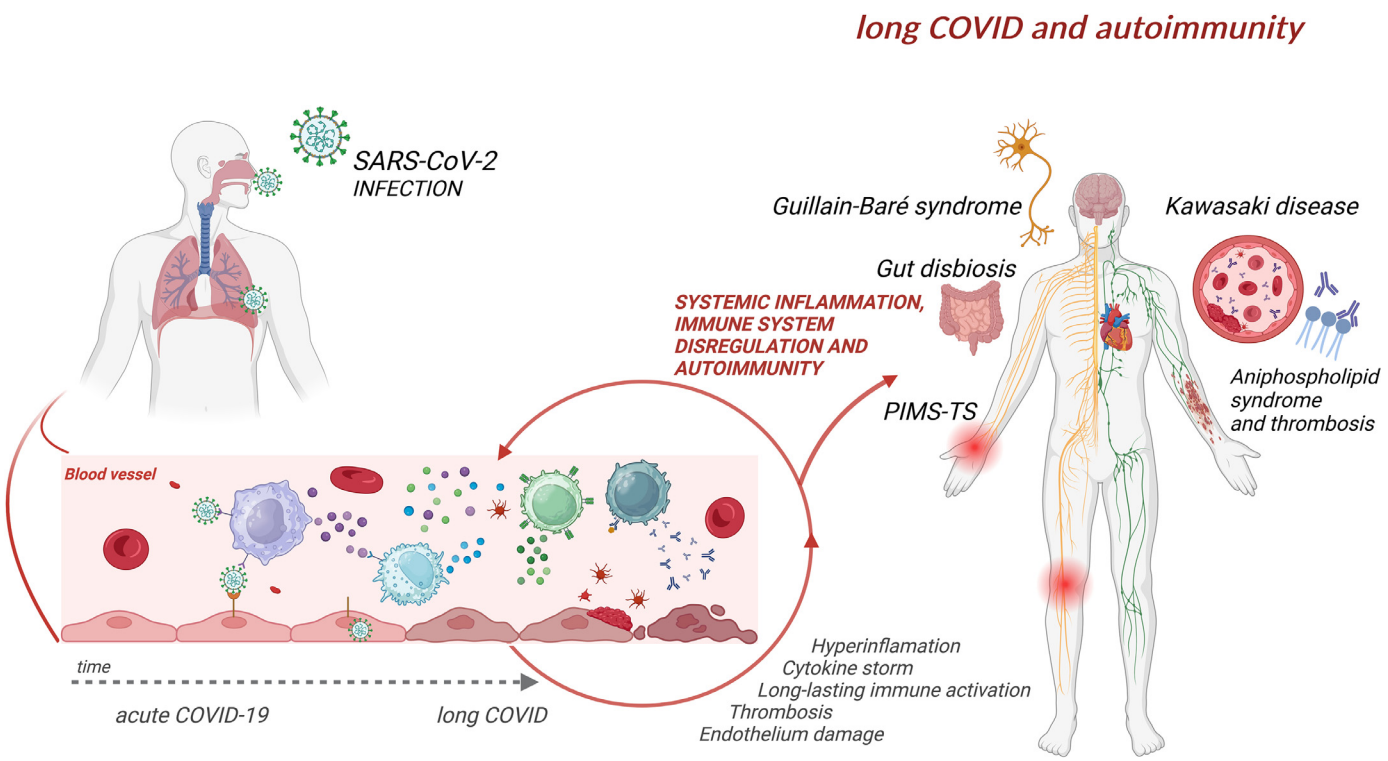

Fig. 1. The connection between SARS-CoV-2 infection and the development of autoimmunity (Created with BioRender.com). SARS-CoV-2 infection may cause long-lasting activation of the immune system and consecutive hyperinflammation and an excessive release of proinflammatory cytokines. This, in turn, together with additional factors (the release of self-antigens from damaged tissues, gut dysbiosis and molecular mimicry) facilitates the development of autoimmunity. PIMS-TS = pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2.

15% of infected individuals requiring hospitalization and oxygen supply at the beginning of the pandemic, to only 3% of cases in 2023.[24] This drop in the number of individuals requiring intensive therapy is caused by changes to SARS-CoV-2 itself, ongoing general immunization, development of vaccination protocols with the first messenger (mRNA)-based vaccine approved in 2020,[25] the emergence of new variants causing milder infections, and changes to testing policies worldwide. Although most COVID-19 convalescents make a full recovery, some experience protracted symptoms that may be associated with past SARS-CoV-2 infection. This phenomenon has been called "long COVID," "post COVID-19," and "postacute sequelae of COVID-19 (PASC)." Among many mechanisms indicated as those responsible for sustained symptoms, autoimmunity draws attention. As has been shown by many researchers, SARS-CoV-2, like other viruses with a confirmed role in developing autoimmunity, can modulate an immune response to facilitate the weakening tolerance to the host's self-antigens, induce autoantibody production due to molecular mimicry, and sustain inflammation which impairs tissues and results in the release of the host's self-antigens as possible targets for an autoimmune response.[26,27] It is important to emphasize that among many possible long-lasting complications of SARS-CoV-2 infection, autoimmunity is of great importance and can contribute to developing long COVID in many individuals (Figure 1).

The interaction between SARS-CoV-2 and the immune system, together with several possible side effects of an autoimmune nature, are described. The number of patients who have recovered from COVID-19 is still growing, and new SARS-CoV-2 variants with altered virulence and transmissibility are still emerging worldwide. This predictably will lead to an increase in the number of individuals suffering from long-lasting complications, including those of an autoimmune nature. Due to this, there is a need for concise description of the subject, which could present the most important aspects of long COVID. The literature about this is very rich, with many excellent research studies and analyses performed by experienced teams that describe the subject in great detail. This narrative review aims to deliver general information about long COVID and related autoimmunity, highlighting selected conditions (antiphospholipid syndrome, Guillain-Barré syndrome and Kawasaki disease). For this purpose, the PubMed/MEDLINE database was searched from 2019 to August 2023 for original articles, systematic reviews, narrative reviews, and meta-analyses (all published in English) with the following combinations of keywords: long COVID AND autoimmunity, long COVID AND epidemiology, long COVID AND symptoms, long COVID AND review, SARS-CoV-2 AND autoimmunity, SARS-CoV-2 AND Guillain-Barré, SARS-CoV-2 AND Kawasaki. Additionally, the PubMed/MEDLINE database was searched for literature describing the biology of SARS-CoV-2 with keywords: SARS-CoV-2 AND genome, SARS-CoV-2 AND infection, SARS-CoV-2 AND (immune OR response), SARS-CoV-2 AND variants. Some information was also gathered from the WHO reports and websites.

Long COVID Definition, Symptoms, and Epidemiology

The term "long COVID" describes the persistent presence of diverse symptoms related to past infection with SARS-CoV-2, often weeks and months after the acute phase of the disease. The symptoms may include those typical for acute COVID-19, as well as entirely new symptoms that emerge following recovery. Since there are no distinct criteria for the diagnosis of long COVID, several definitions have been proposed to establish the indications and time frames for better distinction between acute and long COVID. One definition of long COVID is that of the presence of symptoms beyond 3 weeks after the initial signs of acute SARS-CoV-2 infection, distinguishing it from postacute COVID-19 (4th-11th week) and chronic COVID-19 (12th week and beyond).[28] A similar classification was proposed by the UK National Institute for Health and Care Excellence (NICE), the UK Scottish Intercollegiate Guidelines Network (SIGN), and the UK Royal College of General Practitioners (RCGP), with the first 4 weeks of SARS-CoV-2 infection described as acute COVID-19;

Table 1
The Incidence of the Most Frequent Long COVID Symptoms Described in Systematic Reviews

				Respiratory tract (%)			Neurology (%)		Other (%)		
	Number of participants	Median of age (years)	% of women	Dyspnea	Cough	Reduced lung capacity	Concentration disorder	Anosmia dysgeusia	Joints pain	Chronic fatigue	Chest pain
Groff et al.[43]	250,351	54	44	30	13	30	24	13	10	37	13
Sanchez-Ramirez et al.[44]	5323	55	44	32	13	39	NR	NR	38	16	NR
Nalbandian et al.[45]	3398	57	47	34	15	NR	NR	13	16	53	13
Michelen et al.[46]	10,951	56	48	25	NR	26	26	NR	NR	31	NR
Lopez-Leon et al.[47]	48,009	52	55	24	19	10	27	23	19	58	16
Garg et al.[48]	6924	52	77	43	20	NR	NR	24	27	66	17
Kessel et al.[49]	3000	46	NR	29	36	NR	NR	16	NR	47	22

There is a broad spectrum of different symptoms related to long COVID. In this table, we gathered the most common symptoms reported by a total of 327,956 COVID-19 convalescents in 7 systematic reviews.
NR = not reported.

from 5 to 12 weeks as "ongoing symptomatic COVID-19″; and beyond 12 weeks as "post-COVID-19″ in the case of persistent symptoms.[29] A complex study resulting in the creation of the clinical definition of long COVID was performed by the WHO using the Delphi consensus-based methodology.[30] The term "long COVID" was defined as the development of symptoms in individuals with confirmed or probable infection with SARS-CoV-2, while the time between recovery and 3 months has been defined as "post-COVID-19.″ The symptoms should appear or be sustained during the 3 months following recovery from the acute phase of infection and last for at least 2 months with persistent or fluctuating severity. They also negatively impact on everyday life and have no connection to other known medical conditions. The long COVID diagnosis does not depend on the individuals' viral status, with most of the patients being PCR-negative at the time of diagnosis.[31,32] An effort is still being made to evaluate the prevalence of long COVID. However, the heterogeneity of study groups and methodology makes assessing this difficult. The persistence of symptoms following infection is described in some studies in relation to age, sex, disease severity, and follow-up time. Among COVID-19 patients discharged from hospitals in Michigan in the United States, almost 33% declared persistent symptoms in a 60-day follow-up study.[33] In comparison, in another study in France with a 60 day follow-up time, around 66% of convalescents with noncritical COVID-19 declared persistent symptoms, and almost 33% reported feeling worse than during the acute phase of infection.[34] The studies showed a significant difference in the number of individuals with long COVID between those treated as outpatients (10%-30%) and those who required hospitalization (50%-80%), as well as vaccinated individuals.[35-41] The clinical symptoms related to long COVID are incredibly heterogeneous and include the respiratory and gastrointestinal tracts, joints, central and peripheral nervous system, bone marrow, endocrine system, etc.[42] General symptoms like fatigue are also broadly reported. This heterogeneity comes from a vast number of reports engaging many individuals, thus, it is important to point out the most common symptoms. The incidence of the most frequent symptoms described in systematic reviews is listed in Table 1.[43-49]

Risk Factors of Long COVID

There are several risk factors of long COVID described in the literature. Data collected from 4182 COVID-19 convalescents showed a positive correlation between the risk of developing long COVID and female sex, increasing age, increased body mass index (BMI), and the occurrence of over 5 symptoms in the acute phase of the disease.[50] There is no single explanation of why female sex is a risk factor. However, the role of genetic, hormonal, and environmental differences in innate and adaptive immune responses between females and males is likely to be relevant.[51] Due to these variations, females maintain stronger inflammatory responses and are generally more susceptible to the development of autoimmune diseases, with both phenomena playing an important role in the development of symptoms of long COVID.[52] However, due to the same differences, males are more likely to develop the severe form of acute COVID-19, which is described as an independent risk factor of long COVID.[53] Increasing age and obesity (increased BMI and waist-hip ratio) are often accompanied by other comorbidities such as hypertension and type 2 diabetes, which have a negative health impact prior to the onset of COVID-19, thus worsening the disease outcome and increasing the prevalence of long COVID.[54-57] Other diseases, particularly those of the respiratory tract such as bronchial asthma, and conditions treated with immunosuppressive drugs may also put patients at increased risk of long COVID.[53] Since many symptoms of long COVID are related to an exaggerated inflammatory response, the severity of the acute phase of COVID-19 is associated with a higher risk of developing long COVID, especially for patients who required intensive care and mechanical ventilation.[58] Additionally, increased viral load during the acute phase of infection may increase the incidence of persistent symptoms due to stimulation of the immune system, resulting in extensive tissue damage and viral persistence.[55] Some studies have reported the persistent presence of viral RNA in feces and the nasopharynx in COVID-19 convalescents who developed a humoral response with sufficient production of neutralizing antibodies.[59,60] Additionally, autopsies performed on COVID-19 patients several weeks after the disease outcome showed SARS-CoV-2 RNA in pneumocytes and endothelial cells.[61] One study with 203 post-symptomatic COVID-19 convalescents tested for the presence of viral RNA in the nasopharynx at 2 time points after their recovery found that 12.8% and 5.3% were positive for the coronavirus RNA at the 23rd and 90th day, respectively.[62] Moreover, there were no differences in neutralizing antibody levels between patients with and without viral RNA. However, the former presented a strengthened $CD8^+$ *T* lymphocyte-dependent antiviral response. These findings indicate that in some individuals persistent viral replication is maintained, which in turn leads to sustained activation of the immune system. This results in chronic hyperinflammation, causing subsequent tissue damage.[63] There is evidence that among patients in the acute phase of COVID-19 infection, latent viruses, including Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Herpes simplex virus type 1 (HSV-1), and Human herpesvirus (HHV-6 and HHV-7) can be reactivated. This has a potentially negative impact on disease severity and the risk of developing long COVID.[55,64-66] For the list of long COVID risk factors, see Table 2.

COVID-19 and the Innate Immune System

SARS-CoV-2, like other human viruses, is an obligate intracellular pathogen that uses the host's own cells to replicate and subsequently spread in the environment. It belongs to the group of coronaviruses, which also includes SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), that are responsible for mild to severe infections in humans.[67,68] The SARS-CoV-2 virion contains several surface proteins. The spike protein (S protein) with the receptor binding domain

Table 2
Risk Factors of Developing Long COVID

Female sex
Increasing age
Increased BMI, comorbidities related to obesity: diabetes, hypertension
Respiratory tract disease (e.g., bronchial asthma)
Immunosuppression
Severe form of the acute phase of COVID-19 with the presence of more than 5 symptoms
Increased viral load during the acute phase of COVID-19
Persistent SARS-CoV-2 replication
Reactivation of latent viral infections (e.g. EBV, CMV, HSV-1, HHV-6, HHV-7)

The table summarizes the risk factors of long COVID, described in detail in the text. BMI = body mass index; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV = human herpesvirus; HSV = herpes simplex virus.

(RBD) is used to infect cells via the hosts' angiotensin-converting enzyme 2 receptor (ACE2).[69-71] The viral envelope (E) and membrane (M) structural proteins are essential to the process of assembling new virions. An effective entry to the cell requires the host cell surface transmembrane serine protease 2 (TMPRSS2), responsible for proteolytic cleavage of the S protein, to permit fusion between the virus and the cell.[72,73] Expression of ACE2 and TMPRSS2, therefore, makes host cells prone to coronavirus infection and has been described in many tissues and organs in the body, including the epithelial cells of the respiratory system, type II pneumocytes in pulmonary alveoli, endothelium, liver, kidney, enterocytes, placenta, glial cells, and platelets.[74-85] The SARS-CoV-2 virus binds ACE2 with higher affinity than SARS-CoV. This phenomenon may explain its high infectiousness and ability to cause a pandemic.[86,87]

Viral entry to the cells triggers different pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs), which are responsible for triggering the complex cascade of different proteins to induce an innate antiviral response. The Toll-like receptor 3 (TLR3), TLR7, and TLR 8 are located in the membrane of endosomes', while RIG-like receptors (RLR), RIG-I, and melanoma-associated differentiation-associated gene 5 (MDA5) can be found in the cytosol in most of the tissues including the epithelium.[88] After binding viral RNA, endosomal TLRs polymerize their cytoplasmic tails, thus activating the whole chain of reactions involving various protein kinases, which results in the activation of transcription factors: nuclear factor kB (NF-kB), interferon response factor 3 (IRF3), and IRF7. NF-κB is responsible for activating inflammatory responses by enhancing the expression of genes for tumor necrosis factor (TNF), interleukin (IL)−1, chemokines (CCL2 and CXCL8), and the adhesion molecule E-selectin.[88-90] The crucial interferon-mediated response is triggered by cytosolic RLRs through IRF3 and IRF7. After binding viral RNA RIG-I and MDA5 are bonded by the mitochondrial antiviral-signaling protein (MAVS) to the outer layer of the mitochondrial membrane. By doing so, they initiate the recruitment of TNF receptor-associated factor 3 (TRAF3), TRAF family member-associated NF-κB activator (TANK)-binding kinase 1 (TBK1), and inhibitor of nuclear factor κB (IκB) kinase-ε (IKKε), an activator of different transcription factors (for example IRF3, IRF7, and NF-κB), thus, promoting expression of the type I interferons (IFN-α and IFN-β) and a group of early interferon-stimulated genes (early ISGs)[91,92] (Figure 2). Type I IFNs stimulate the expression of hundreds of genes that encode products for creating potent antiviral reactions. This process is a cascade consisting of different factors and signal transmitters. The Jak tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1) are activated by the complex of IFN-I and IFN-alpha and beta receptor (IFNAR).[93] An active TYK2 and JAK1 then phosphorylate the signal transducer and activator of transcription 1 (STAT1) and STAT2. These transducers are responsible for forming a complex called IFN-stimulated growth factor 3 (ISGF3) consisting of STAT heterodimers and IRF9. Subsequently, the ISGF3 binds to particular sequences in the ISG promoters called IFN-stimulated response elements (ISREs). This leads to the activation of ISG transcription. One of these genes encodes protein kinase receptor (PKR), which can detect viral dsRNA synthesized during viral replication and completely halt all translational processes in the cell.[94] Another antiviral mechanism induced by IFN-I includes the expression of cytosolic enzymes, which can degrade viral nucleic acids or cause mutations in their sequence, as well as production of proteins that can interfere with releasing new viral particles from infected cells, thus restricting infection in nearby cells.

IFN in SARS-CoV-2 Infection

Since viral-induced IFN-dependent responses engage hundreds of genes, some of which are responsible for cell survival processes, its overreaction can be dangerous to a host. Due to this, the whole mechanism must remain under strict host control. Distinct viruses can induce IFN synthesis with various strengths and evolve many different mechanisms to counteract it. Studies evaluating the level of IFN-I response triggered by SARS-CoV-2 on cell and animal models showed, that the coronavirus induces a milder response in comparison to other respiratory viruses.[95] At the same time the virus can evade this response using distinct mechanisms.

Inhibition of IFN Pathway

Viral strategies to counteract IFN-dependent responses are focused on inhibiting of IFN-I production and preventing signal transduction to surrounding cells. To do so, the virus inhibits all proteins and signal pathways leading to IFN-I synthesis in host cells. Several SARS-CoV-2 proteins engaged in this process have been identified. The recognition of viral RNA by RIG-I and MDA5 can be inhibited by several viral nonstructural proteins (NSP10, NSP14, NSP15, NSP16),[96-98] while NSP1 can enhance the degradation of the host's mRNA encoding the IFN molecule.[99] The viral open reading frame (ORF) proteins interfere with RLRs and TLRs signal transduction by blocking MAVS or MAVS together with TRAF3 and TRAF6 proteins (ORF3b and ORF9b, respectively) and IRF3 signal transducer (ORF6).[100,101] The ORF3a can enforce IFNAR degradation, while proteins NSP1 and ORF6 interact with STAT-dependent signal transduction, thus blocking IFN-I induced ISG expression.[102] The virus can also use the host's own regulatory mechanism involved in IFN pathway control to counteract its activation. For example, the expression of the suppressor of cytokine signaling 3 (SOCS3) can be intensified by viral S protein in B lymphocytes, leading to degradation of IRF7 as well as inhibition of JAK-STAT signal transduction[103] (Figure 3).

Cells in the Innate Immune Response in COVID-19

The chemokines secreted in response to infection initiate the recruitment of innate immune cells: dendritic cells (DCs), macrophages, and neutrophils, which cooperate hand in hand with both IFNs and adaptive immunity in fighting the infection.[104] These cells react to the presence of soluble factors by releasing a broad set of molecules to orchestrate the immune response. The NF-κB-dependent mediators can

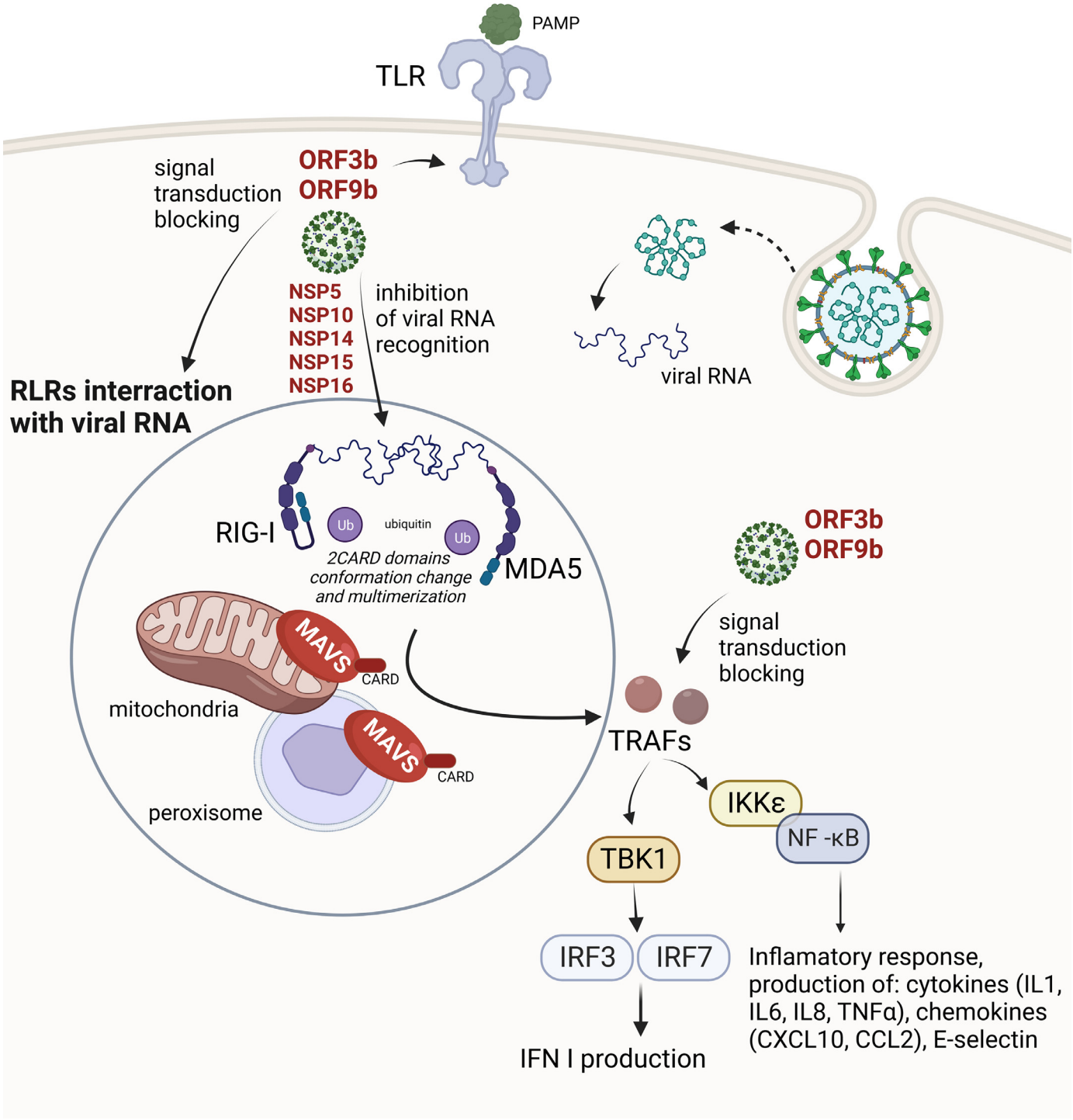

Fig. 2. The pathways of the inflammatory response activation triggered by the entry of SARS-CoV-2 to the cells (Created with BioRender.com). Interaction between SARS-CoV-2 proteins and PRRs triggers the production of IFNs and proinflammatory cytokines. This is an important part of antiviral innate immune response. However, SARS-CoV-2 has the ability to evade this response by blocking its antigens recognition and signal transduction in the cascades (see text for details). CARD = caspase activation and recruitment domain; CCL2 = monocyte chemoattractant protein 1; CXCL10 = interferon-γ-induced protein of 10 kDa; IKKε = inhibitor of nuclear factor κB (IκB) kinase-ε; IL=interleukin; IFN = interferon; IRF = interferon response factor; MAVS = mitochondrial antiviral-signaling protein; MDA5 = melanoma-associated differentiation-associated gene 5; NF-kB = nuclear factor kB; NSP = nonstructural protein; ORF = open reading frame protein; PAMP = pathogen-associated molecular pattern; PRRs = pattern recognition receptors; RIG-*I* = retinoic acid-inducible gene-I; RLR = RIG-like receptor; TBK1 = TRAF family member-associated NF-κB activator (TANK)-binding kinase 1; TLR = Toll-like receptor; TNFα = tumor necrosis factor α; TRAF = TNF receptor-associated factor; Ub = ubiquitin.

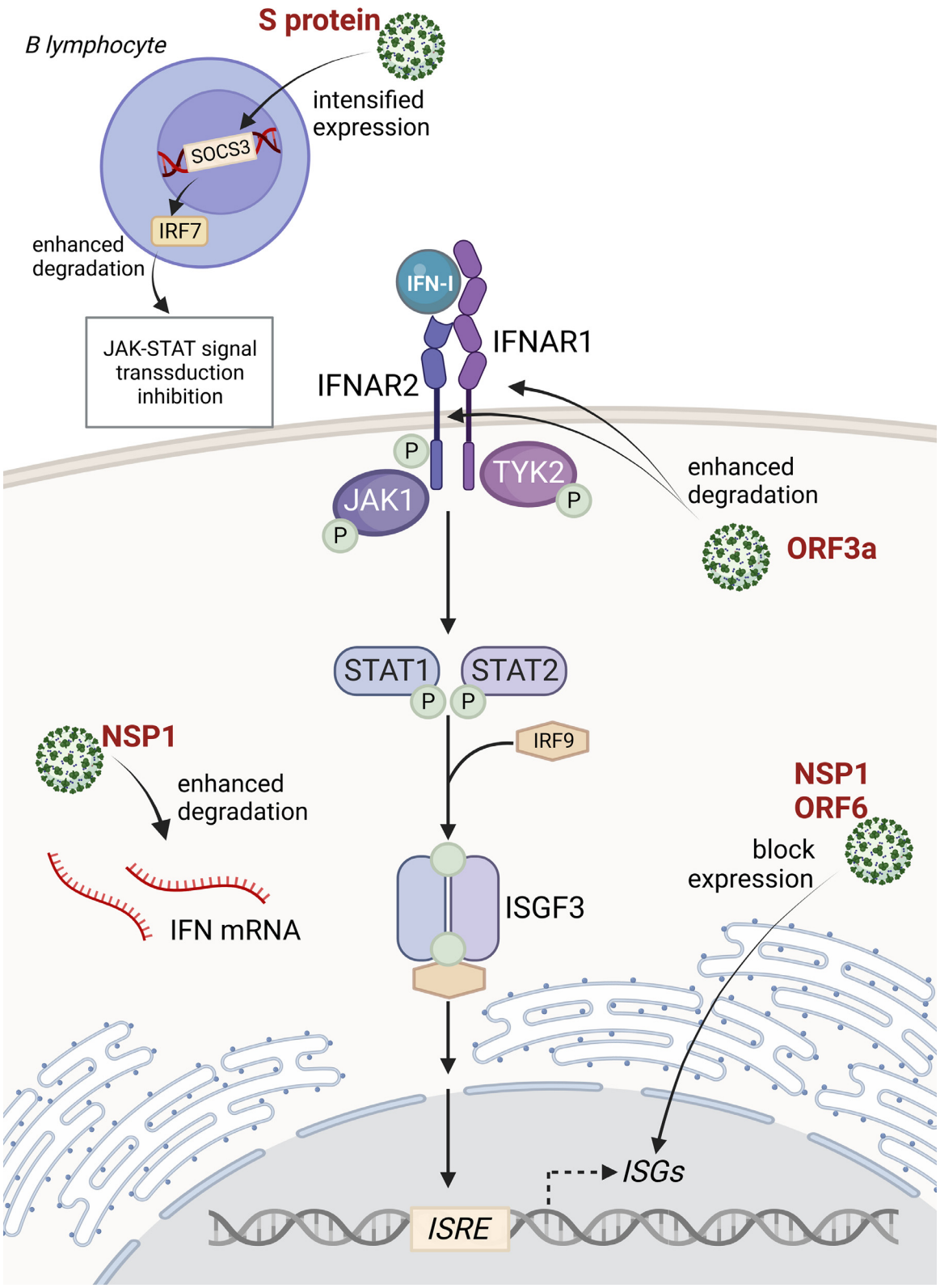

Fig. 3. SARS-CoV-2 can block the expression of ISGs and weaken antiviral innate immune response (Created with BioRender.com). Viral proteins can interfere in the transduction of the signal from IFNARs to the nucleus and directly block the expression of ISGs. IFN-*I* = interferon type I; IFNAR = complex of IFN-I and IFN-alpha and beta receptor; IRF7 = interferon response factor 7; ISGF3 = IFN-stimulated growth factor 3; ISGs = interferon-stimulated genes; ISRE = IFN-stimulated response element; JAK1 = Janus kinase 1; mRNA = messenger RNA; NSP = nonstructural protein; ORF = open reading frame; SOCS3 = suppressor of cytokine signaling 3; STAT = signal transducer and activator of transcription; TYK2 = Jak tyrosine kinase 2.

attract macrophages and neutrophils to the site of infection.[105] Therefore, the evidence shows an increased number of CD169$^+$ macrophages, with high ACE2 expression, containing viral N protein in the respiratory tract, spleen, and lymph nodes of infected individuals.[106,107] These macrophages, together with mast cells, epithelial, and endothelial cells, are the prominent but not the only source of proinflammatory mediators and chemokines (for example, IL-1, IL-2, IL-4, IL-6, IL-17, TNF, IFNγ, CCL2, CCL3, CCL5, CXCL8, CXCL9) found in both: bronchoalveolar lavage fluid (BALF) as well as in blood.[108-113]

Alteration in Nonclassical Monocytes

An acute phase of SARS-CoV-2 infection is related to an expansion of intermediate monocytes (CD14$^+$ CD16$^+$), which are a source of proinflammatory IL-6 and, as a result, can create a self-perpetuating loop enhancing inflammation.[114,115] This cell type seems to have a negative impact on the disease severity since its highest expansion was observed in patients who required intensive care treatment.[116] Together with the recovery, however, there is a shift in monocyte subpopulation in favor of nonclassical monocytes (CD14^{lo} CD16$^+$). These cells, also described as vascular sentinels, caretakers, or patrolling monocytes, are responsible for anti-inflammatory responses and for maintaining vascular homeostasis. They constantly crawl on endothelial surfaces using a lymphocyte function-associated antigen/intracellular adhesion molecule 1 (LFA/ICAM-1)-dependent mechanism and, by means of TLR7, recognize damaged endothelial cells and contribute to cellular debris removal.[117-121] Many studies performed on mice models showed their protective role in conditions related to endothelial injury. Studies showed an interesting behavior of nonclassical monocytes in atherosclerosis. While classical monocytes are essential to start an atherosclerotic plaque formation, nonclassical cells, although recruited to the site of atherogenesis, remained inside the vessel, patrolling the surface of the endothelium.[118,119,122-126] Additionally, in several studies, nonclassical monocytes-deprived mice fed an atherogenic Western diet showed accelerated plaque formation.[127-129] However, there are reports suggesting the opposite conclusion,[130,131] thus, further investigation referring to humans is needed. The protective role of nonclassical monocytes was also suggested in diminishing vasculature damage in kidneys[132,133] and heart.[134,135] An increased number of this specific subpopulation was found in patients with long COVID in comparison to healthy controls.[129] Although they are generally considered anti-inflammatory and vascular protective cells, there is some evidence suggesting their potentially ambiguous role in certain autoimmune-mediated diseases such as lupus erythematosus,[136-139] rheumatoid arthritis[140-142] and demyelination in the central nervous system.[143,144] It was also proven that nonclassical monocytes, which migrate to tertiary lymphoid organs (TLOs) and express programmed cell death protein 1 (PD-L1) molecules, may intensify T lymphocytes apoptosis through a PD-1/PD-L1 (programmed cell death ligand 1) mechanism.[145] This may have a negative impact, especially when it accompanies inflammation or oncogenesis.

Cytokine Storm in COVID-19

Acute COVID-19 infection is characterized by a significant release of proinflammatory cytokines, particularly IL-6. This is not only one of the main proinflammatory mediators but also the cytokine responsible for the amplification of the inflammatory process.[107,146] This phenomenon, described as a "cytokine storm," is more common in critically ill COVID-19 patients compared to those with milder symptoms, and is a poor prognostic indicator.[147-152] The ability of SARS-CoV-2 to induce excessive cytokine release is attributable to the interaction of the viral S protein with ACE2 receptors on host macrophages and endothelial cells, which induces the intracellular NOD (nucleotide-binding oligomerization domain)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome.[153] This happens in different ways: for example, the virus impairs the mitochondrial respiratory chain inside cells, thus causing increased production of reactive oxygen species (ROS).[154,155] The viral N protein causes activation of the complement system, which releases the anaphylatoxins C3a and C5a and forms the membrane attack complex (MAC).[154] Additionally, the use of the cellular ACE2 receptor results in an alteration to the synthesis of specific forms of angiotensin.[156] As a result of this activation of the NLRP3 inflammasome, proinflammatory cytokines (IL-1β, IL-18) are released, leading to cell injury and death via pyroptosis.[157] An inflammasome is a complex composed of different proteins, which also contain NOD-like receptors for PAMPs. This complex can activate caspase enzymes. The formation of the NLRP3 inflammasome results in the activation of caspase-1 via the proteolysis of IL-1β and IL-18[158] (Figure 5). As inflammasomes can detect PAMPs and form larger aggregates, they are an important player in the innate immune response. By inducing inflammation, they are often able to eliminate or at least limit the spread of an invading pathogen.[159] Inflammasome activity needs to be strictly regulated, as uncontrolled activation may facilitate the development of conditions such as Alzheimer's disease, gout, atherosclerosis, and autoinflammatory diseases.[160]

The source of the first wave of proinflammatory cytokines in COVID-19 is still uncertain. Studies have excluded classical DC, M1, and M2 macrophages as a relevant source of proinflammatory mediators in the acute phase of infection with SARS-CoV-2, even though these cells were prone to infection.[161-164] There is evidence that neutrophils can play an important role in generating proinflammatory cytokines. Aymonnier et al.[165] reported that during the acute phase of COVID-19, an NLRP3 inflammasome can be effectively activated in neutrophils. The role of IL-1 in inducing the cytokine storm is noteworthy as it may enhance the transcription of its own genes as well as those of other proinflammatory cytokines.[166-169] This would amplify the production of inflammatory mediators. Excessive proinflammatory cytokine release, particularly IL-1, IL-6, TNF, and IFNs, may result in endothelial and epithelial cell damage. This can cause multiorgan injury, as well as disseminated intravascular coagulation (DIC) and thrombosis.[170-178] A significant number of deaths among COVID-19 patients was due to ARDS, which is also a common feature of infection with SARS-CoV and MERS-CoV.[110,179] This pulmonary involvement can be at least partially explained by the inflammation-related impairment of the membrane between alveoli and capillaries resulting in pulmonary edema and respiratory failure.[180,181] The direct viral injury of the endothelium and myocardium, together with a severe proinflammatory shift in the immune system, may also lead to a variety of cardiovascular symptoms and worsen disease outcomes.[182,183] COVID-19 patients were developing direct myocardial damage (ischemia, myocardial infarction, myocarditis) as well as a broad spectrum of arrhythmias with possible cardiogenic shock.[6,184-189] There are reports indicating renal involvement, including acute kidney injury (AKI) and secondary complications (electrolyte and acid-base imbalance, hypertension), with laboratory findings such as proteinuria and hematuria.[10,11,190,191] The ability of SARS-CoV-2 to infect neurons, astrocytes, and microglia and, as a consequence, to activate inflammasomes in the central nervous system may play a role in neurological complications due to ongoing inflammation and related tissue injury.[192,193]

Adaptive Immunity in COVID-19

An adaptive immune response with its cytotoxic effect and neutralizing antibody production is required for efficient and complete elimination of the virus. A cytotoxic effect is provided by CD8$^+$ lymphocytes, whereas different subclasses of CD4$^+$ lymphocytes act as enhancers or regulators as well as coordinate the adaptive humoral response against SARS-CoV-2, which leads to the presence of IgM, IgG, and IgA class antibodies in patient's serum.[194,195] The research of Tarke et al.[196] performed on COVID-19 convalescents indicated immunodominance of several SARS-CoV-2 proteins (including NSP3, NSP4, NSP12, S, M, N, and ORF3a) which were responsible for the majority of CD4$^+$ and CD8$^+$ *T*

cell responses. In the humoral response, the neutralizing antibodies are directed against the viral S protein (and its RBD) as well as against proteins forming the nucleocapsid.[197-202] It has been indicated by Suthar et al.[203] that the production of neutralizing antibodies in the acute phase of COVID-19 is rapid, with the presence of detectable titers of specific antibodies on average on the 6th day after PCR confirmation of the infection. Additionally, the authors showed quick antibody class switching into IgG with a predominance of IgG1 and IgG3 subclasses in serum.[203] An important role of SARS-CoV-2 specific IgA neutralizing antibodies, present on the mucosal membranes in the respiratory tract, has been shown by Quinti et al.,[204] who describe its role in preventing the virus from infecting epithelial cells. Except for interrupting the process of infecting new cells by blocking crucial viral proteins, antibodies also coordinate antibody-dependent cell-mediated cytotoxic effect (ADCC) and cellular phagocytosis (ADCP), as well as complement-dependent cytotoxicity (CDC).[205]

T Cells Exhaustion and t_{cm} Decrease

An antiviral response relies, among others, on the activity of $CD8^+$ *T* lymphocytes and natural killer (NK) cells, which act as the effector and process-regulating cells. The decreased count of $CD4^+$, $CD8^+$, and NK lymphocytes, and their functional exhaustion related to the disease severity is caused by the inflammation-related acceleration of apoptosis.[206-212] Additionally, the cells continued to present exhaustion features after the patients' recovery and restoration of their amount. This observation may indicate the potential ability of SARS-CoV-2 to weaken the antiviral immune response.[106,209,213,214] Among patients presenting symptoms of long COVID, an elevated number of exhausted $CD4^+$ and $CD8^+$ *T* cells was described in comparison to the disease convalescents and healthy controls, whereas the number of $CD4^+$ *T* central memory cells (T_{CM}) was decreased.[129,215] However, the production of the intracellular proinflammatory cytokines (IL-2, IL6, and IL-4) was found to be increased in both $CD4^+$ and $CD8^+$ cells of long COVID patients compared to healthy controls and convalescents without persistent symptoms.[129]

SARS-CoV-2 Variants and Immune Response

An emergence of virus variants is caused by errors occurring during viral genome replication[216] and due to editing and modification of viral RNA done by the host's own cellular enzymes: apolipoprotein B mRNA editing catalytic polypeptide-like enzyme (APOBEC) and adenosine deaminase RNA specific 1 enzyme (ADAR1)[217] (Figure 4). APOBEC and ADAR1 are responsible for cytosine-to-uracil and adenosine-to-inosine substitution in viral RNA, respectively.[218,219] They are a part of the host's antiviral innate immune defense system. However, they can be used by a virus for the creation of new variants.[220] This results in nucleotide sequence changes, which sometimes may either facilitate or impede viral replication and transmission, as well as the virus' ability to escape from the host's immune response.[221] SARS-CoV-2 variants may be described as variants of concern (VOC) and variants of interest (VOI) defined by the WHO in the report published in 2021.[222] According to this document, VOC is defined as a variant with increased transmissibility and virulence, which negatively influences epidemiology and clinical presentation. Another feature defining VOC is the decreased effectiveness of preventive measures, therapy, and vaccination against it. In comparison, VOI is described as a variant that differs phenotypically from the standard isolate and has been found to cause multiple cases of COVID-19 in clusters or worldwide. A viral S protein is a main target for neutralizing antibodies that have been elicited by either SARS-CoV-2 infection or vaccination.[199,223,224] Thus, genetic mutations leading to changes in its structure are responsible for the virus escaping from the humoral immune response. The details of VOCs are presented in Table 3.[225–227]

Autoimmunity and COVID-19

Infection with SARS-CoV-2 seems to promote the autoimmune phenotype, particularly in genetically predisposed individuals. There are several mechanisms involved in this process, which are typical not only for the coronaviruses but also for other viral infections, including EBV, CMV, rubella virus, hepatitis B and C viruses (HBV, HCV), human immunodeficiency virus (HIV), and human T lymphotropic virus (HTLV).[27,229-232] One of these mechanisms is the loss of tolerance to self-antigens due to infection-related lymphopenia, a state that consequently facilitates the development of autoimmune processes by enhancing the proliferation of T lymphocytes that recognize self-antigens.[233] Additionally, a decrease in suppressor T lymphocytes ($CD3^+$, $CD8^+$, $CD28^+$) as well as increased regulatory T lymphocytes ($CD3^+$, $CD4^+$, $CD25^+$, $CD45^+$, $CD127^{lo}$) was noted in severe cases of COVID-19.[234] Another mechanism is hyperinflammation and its consequences of tissue damage with an exposition of new antigens and bystander activation of autoreactive T lymphocytes by activated dendritic cells.[235] Molecular mimicry also plays a significant role in the induction of autoreactivity.[236] Over 30 protein SARS-CoV-2 antigens have been described so far, which share parts of their linear sequence with humans. There is a high probability that antibodies against the viral antigens may interact with the host's self-antigens, thus triggering the autoimmune process.[237] An excessive release of cytokines in the acute phase of COVID-19 leads to the release of neutrophil extracellular traps (NETs) and intracellular enzymes.[238] The released traps are a prominent source of self-antigens (DNA, histones, and other chromatin proteins), while enzymes may induce modifications of the host's proteins, thus turning them into targets for an autoreactive humoral response.[239] The hyperinflammation related to COVID-19 and the use of different drugs, including antibiotics as treatment, leads to dysbiosis or changes to the human gut microbiome. These changes to the microbiome may, in turn, enhance hyperinflammation due to the altered release of gut bacteria-derived mediators, which negatively modulate the host's immune response.[240,241] Studies have found similarities in qualitative and quantitative gut microbiome changes in COVID-19 patients and those suffering from autoimmune diseases (for example, systemic lupus erythematosus [SLE]) compared to healthy controls. For example, decreased microbiome diversity and a shift in dominant bacteria have been reported to have a negative impact on COVID-19 patients by favoring severe forms of the disease.[242-247]

The detection of distinct autoantibodies is the most commonly used method to discern an autoimmune phenotype. As SARS-CoV-2 can induce hyperinflammation with subsequent immune system alterations and tissue damage, followed by a release of self-antigens, the development of various autoantibodies is likely. Studies were performed for the detection of autoantibodies and for establishing their specificity. Rojas et al.[248] tested 100 COVID-19 adult convalescents and 30 control healthy individuals for a broad spectrum of autoantibodies in both the IgG and IgM isotypes. Autoantibodies against thyroglobulin, classic antinuclear antibodies ANA (anticentromere, anti-La/SS-B, antihistone, anti-PL7, anti-U1snRNP), and anti-GAD65 (glutamic acid decarboxylase 65) were found, as well autoantibodies against a broad spectrum of IFNs.

Antiphospholipid Antibodies in COVID-19

There is evidence that infection with SARS-CoV-2 may result in the production of prothrombotic antiphospholipid antibodies (APLAs). Pascolini et al.[249] tested unwell COVID-19 patients and non-COVID-19 patients for the presence of APLAs. This included anti-β2-glycoprotein I (β2-GPI) and anticardiolipin (aCL). In the group of patients with COVID-19, the authors reported an incidence of 9.1% and 24.2%, respectively, while in the control group there was only 1 participant (4%) positive for IgG aCL autoantibodies. Other studies, including COVID-19 patients who were admitted to hospitals due to the severity of the disease, have reported similar findings.[250,251] They all found a higher prevalence of

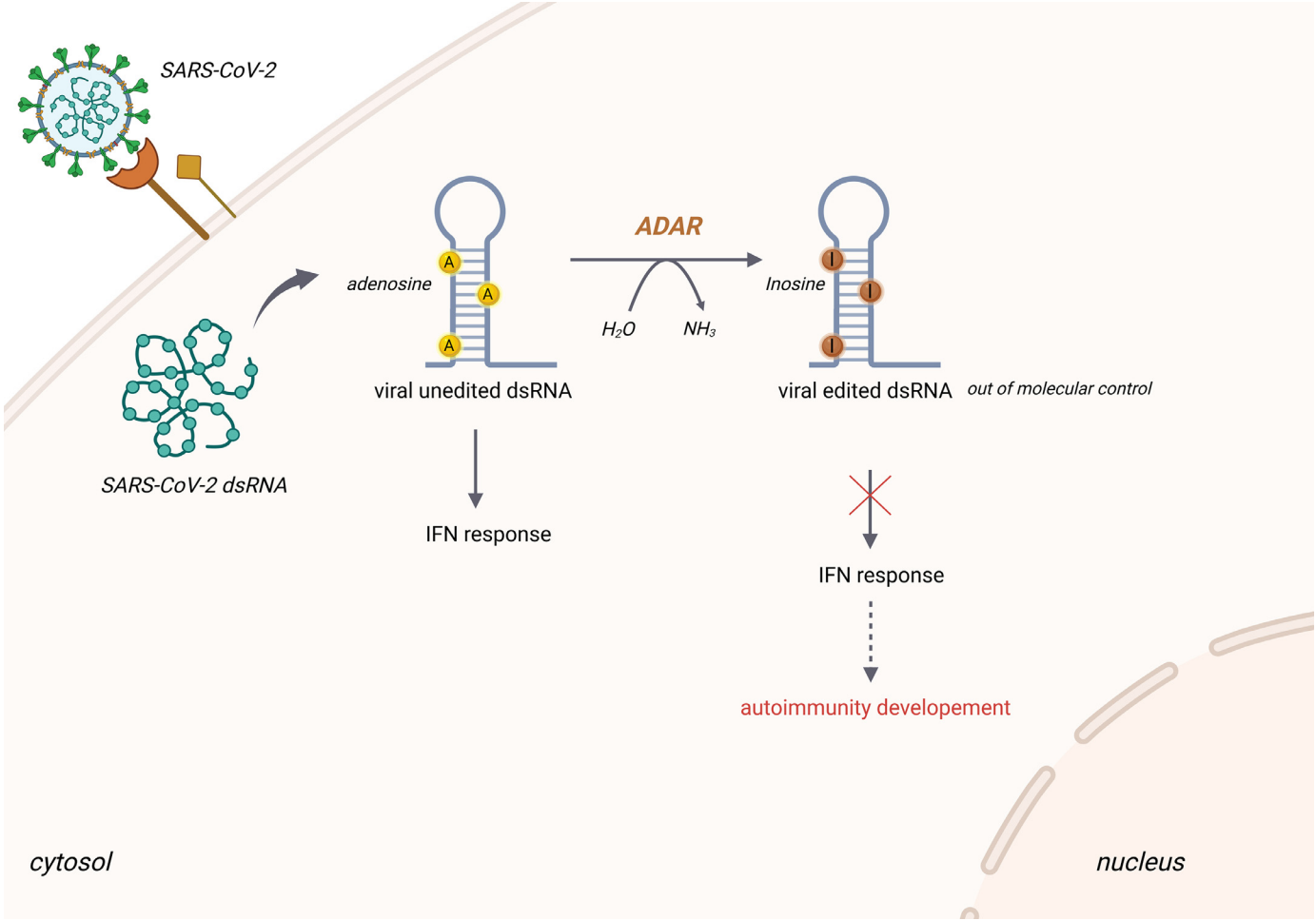

Fig. 4. The role of ADAR in changing nucleotide sequence in viral RNA (Created with BioRender.com).
ADAR is responsible for changing adenosine into inosine in viral RNA. This, in turn, weakens the IFN production and facilitates the development of new SARS-CoV-2 variants. ADAR = adenosine deaminase RNA specific 1 enzyme; dsRNA = double-stranded RNA; IFN = interferon.

Table 3
The VOCs Characteristic

WHO label	PANGO Lineage[228]	Viral proteins (its domains) with mutations	Effect on transmissibility	Effect on virulence	Vaccines efficacy
Alpha	B.1.1.7	S (RBD and NTD), NSP6, N	Increased	Increased	Decreased
Beta	B.1.351	S (RBD and NTD)	Increased	Increased	Decreased
Delta	B.1.617.2	S (RBD and NTD), ORF1a/b, ORF3, ORF7a, N	Increased	Increased	Decreased
Gamma	P.1	S (RBD and NTD)	Increased	Increased	Decreased
Kappa	B.1.617.1	S (RBD and NTD), ORF1a/b, ORF3, ORF7a, N	Increased	Unknown	Decreased
Omicron	B.1.1.529	S (RBD and NTD)	Increased	Decreased	Decreased

The mechanism responsible for an increase of transmissibility, virulence, and a decrease of the efficacy of the different types vaccines is the change of the virus' S protein (in its RBD and NTD domains) and additional mutations in ORF, NSP, and N proteins.
NSP = nonstructural protein; NTD = N-terminal domain of protein S; ORF = open reading frame protein; RBD = receptor binding domain of protein S; S = spike protein.

APLAs, particularly lupus anticoagulant (LA) and aCL, in COVID-19 patients compared to control groups or to the prevalence of APLAs in the general population. The APLAs were more often IgA rather than IgM or IgG isotypes. There was a correlation between the presence of APLAs and the severity of COVID-19 disease, although no association was found between APLAs and the risk of thromboembolism. Additionally, Galeano-Valle et al.[252] tested a group of 24 COVID-19 patients with confirmed pulmonary embolism or deep vein thrombosis and found that only 2 (8%) were weakly positive for aCL and β2-GPI. This finding supports the other findings that APLAs do not contribute to thromboembolic complications during the acute phase of COVID-19. All these studies used small cohorts. However, a meta-analysis including 1591 adult COVID-19 patients enrolled in 21 studies reported similar findings.[251] The prevalence of APLAs among participants was high (46.8%), with LA being the most frequent antibody (50.7% of all APLAs), while no association between APLA positivity and COVID-19 severity or thromboembolism occurrence was found. Also, of interest is the persistence of APLAs following recovery, as according to revised antiphospholipid syndrome (APS) diagnostic guidelines from a conference in Sapporo, Japan only the persistent presence of APLAs can be considered to be a serologic marker of APS.[253] Ghilardi et al.[254] performed a prospective study including COVID-19 patients admitted to the intensive care unit due to disease severity. At admission, the prevalence of LA, aCL, and β2-GPI was 36.5%, 12.5%, and 15.6% respectively, which is comparable to previously described con-

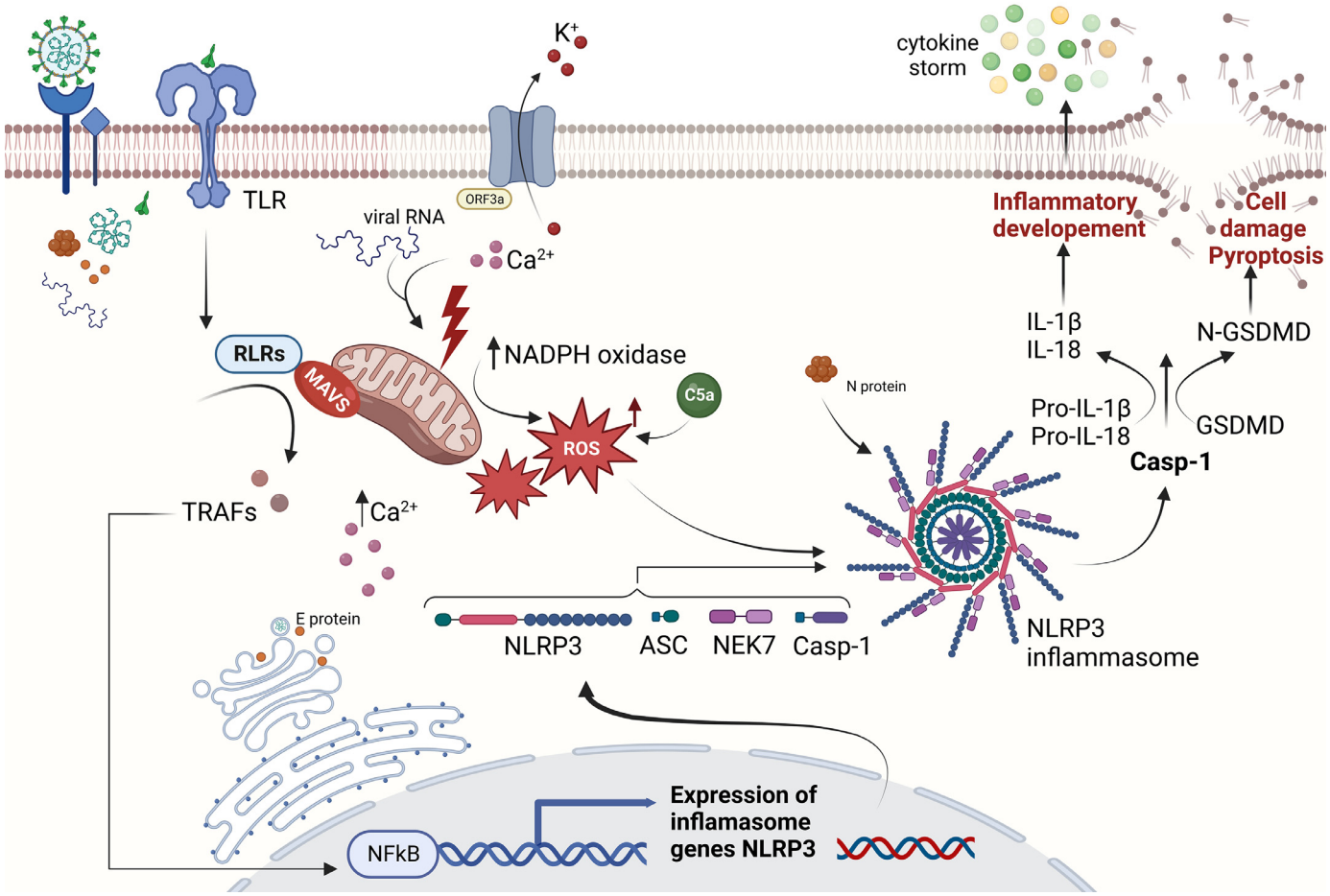

Fig. 5. SARS-CoV-2 induces the formation of NLRP3 inflammasome (Created with BioRender.com).
An activation of inflammasome by SARS-CoV-2 in different mechanisms is responsible for an excessive release of proinflammatory cytokines, tissue damage, and consequently autoimmunity development. ASC = apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; C5a = complement component 5a; Casp-1 = caspase 1; GSDMD = gasdermin D; IL – interleukin; MAVS = mitochondrial antiviral-signaling protein; NADPH = nicotinamide adenine dinucleotide phosphate; NEK7 = NIMA-related kinase 7; NF-kB = nuclear factor kB; N-GSDMD = *N*-terminal fragment of gasdermin D; NIMA = noninherited maternal antigen; NLRP3 = NOD-like receptor family pyrin domain containing 3; ORF = open reading frame protein; RLR = RIG-like receptor; ROS = reactive oxygen species; TLR = Toll-like receptor .

clusions. As in previous reports, the authors did not report an association between APLAs and COVID-19 disease severity. All patients positive for APLAs were re-evaluated for antibody presence after at least 12 weeks following recovery. The titers and prevalence of APLAs were generally lower. Another report from Blickstein et al.[255] estimated APLA prevalence in convalescents from mild COVID-19 to be around 6%. Additional research and studies are required to reach a conclusion however, the evidence currently available suggests that APLAs induced by COVID-19 may be transient in most patients. However, some types of APLAs, especially anticardiolipin antibodies, may be expressed after other viral or bacterial infections.[256] Therefore, their presence cannot always be considered to be a marker of possible APS development, making their contribution to the development of long COVID uncertain.

Vasculitis and Kawasaki Disease in Children

It has been postulated that infection with SARS-CoV-2 may cause some forms of vasculitis as a result of the direct cytotoxic effect of the virus on endothelial cells, as well as an intense immune response and possible involvement of an autoimmune response against vessel walls.[257] Among many case reports describing single individuals with different forms of vasculitis possibly induced by SARS-CoV-2, Kawasaki disease draws special attention. This is an autoimmune-mediated inflammatory disease of medium and small vessels. The highest incidence is in Japan, where there are an estimated 240 cases per 100,000 children under 5 years old.[258] Kawasaki disease has a seasonal pattern in Japan, the highest incidence is in January, June, and July, and the lowest incidence is in October.[259] Differences in prevalence between ethnicities suggest an important role of genetic factors, with the highest prevalence in the Asian population.[260] Viral infections such as EBV, HIV, adenovirus, and parvovirus are known to be triggers of the disease, as they activate the antiviral immune response which engages IFN-dependent pathways and the recruitment of immune cells, thus leading to the development of an inflammatory process within vessels walls.[261,262] An exaggerated immune response, with different cells releasing a broad spectrum of cytokines, may result not only in breaking immune self-tolerance with subsequent autoimmune response against self-antigens but also in weakening the structure of vessel walls. This can lead to the development of an aneurysm, particularly in the coronary arteries in Kawasaki disease.[262-266] Kawasaki disease is one of the most prominent causes of acquired heart disease in developed countries.[267] Ouldali et al.[268] reported an increase in Kawasaki disease incidence among

patients under 18 years hospitalized in a pediatric center in the Paris, France region. There were 1 to 2 cases per month in the 15 years before the SARS-CoV-2 pandemic, compared to 6 cases per month in April 2020 after the peak of COVID-19 incidence in their region. An increase in Kawasaki disease incidence was also reported by Verdoni et al.[269] in the Italian province of Bergamo. There were 19 cases among children during the 5 years prior to the COVID-19 pandemic, compared to 10 cases in 3 months of the first half of 2020, 8 of which had a confirmed SARS-CoV-2 infection. There was not only an increased incidence but also differences in the clinical picture: they reported an older age at the time of diagnosis, a higher rate of coronary artery involvement, and signs of macrophage activation syndrome (MAS). In COVID-19, the symptoms typical of Kawasaki disease are similar to those of hyperinflammation caused by SARS-CoV-2 and are considered to be a part of a bigger clinical picture, where endothelial injury is mediated by the COVID-19-related mechanisms described above. For this reason, there are other names used to describe this phenomenon: multisystem inflammatory syndrome in children (MIS-C) and pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS).[263] This new and potentially life-threatening syndrome may lead to the impairment of vital organs and systems, and it was, therefore, crucial to establish guidelines to help clinicians in the diagnosis and treatment of the condition. Algarni et al.[270] compared previously published guidelines from the WHO, American Centers for Disease Control and Prevention, American Academy of Pediatrics, and American College of Rheumatology in an attempt to unify their recommendations. All guidelines included were consistently specified (below 21 years of age) and fever (documented fever ≥ 38 °C for ≥24 h; or subjective fever for ≥24 h). As signs of endothelial injury, the following laboratory findings were proposed: elevated C-reactive protein (CRP) and ferritin concentration; increased erythrocyte sedimentation rate (ESR); indicators of myocardial injury and cardiac insufficiency (elevated troponin and brain natriuretic peptide [BNP]), and indicators of thrombin generation with consecutive fibrin formation and fibrinolysis (elevated D-dimer and low platelet count). The authors suggested a 4 to 6-week period between SARS-CoV-2 infection and the beginning of MIS-C symptoms, and the presence of symptoms typical of Kawasaki disease with involvement of more than 2 organs, as all guidelines were consistent on this. Knowledge and understanding of the mechanisms underlying the development of MIS-C influenced on recommended therapies, including anti-inflammatory and antiplatelet drugs, which reflect the important role of the inflammatory process and endothelial injury in the pathogenesis of MIS-C. Kawasaki disease related to SARS-CoV-2 infection is more severe compared to classic form of the disease.[271]

Guillain-Barré Syndrome After COVID-19

Guillain-Barré syndrome (GBS) is an acute postinfectious polyradiculoneuropathy caused by the autoimmune-mediated demyelination of nerves. Clinically, it is characterized by symmetrical ascending motor weakness, paresthesia, reduced or absent deep tendon reflexes, and sensory distortions. There are classification systems of GBS based on clinical characteristics (sensorimotor; paraparetic; pure motor; pure sensory; Miller-Fisher syndrome [MFS]; bilateral facial palsy with paresthesia; pharyngeal-cervical-branchial variant; and Bickerstaff brainstem encephalitis) or results of electromyography (acute inflammatory demyelinating polyneuropathy [AIDP]; acute motor axonal neuropathy [AMAN]; and acute motor-sensory and axonal neuropathy [AMSAN]).[272,273] The incidence of GBS has been estimated to be between 1.1 and 1.8 per 100,000 per year. There is a lower incidence in children and an increasing incidence with age up to an estimated 3.3 per 100,000 per year after 50 years of age.[274] In two-thirds of cases, GBS is preceded by either a respiratory or gastrointestinal tract infection.[275] The identified infectious triggers include *Campylobacter jejuni*,[276] *Haemophilus influenzae, Mycoplasma pneumonia*, EBV, CMV, influenza A virus, HSV, HIV, Zika virus,[277,278] and hepatitis E virus.[279,280] Both cellular and humoral immune mechanisms are involved in GBS development. The molecular patterns of infectious agents may resemble gangliosides located in the myelin sheath of nerves.[281] Specific antiganglioside antibodies corresponding to distinct types of the disease can be found in patients with GBS.[275,281] There have been reports of GBS secondary to MERS-CoV infection,[282] a coronavirus that shares genetic homology with SARS-CoV-2. As such, the possible role of SARS-CoV-2 in causing GBS during the pandemic has been taken into account. A systematic review by Aladawi et al.[283] includes 109 individuals with confirmed or suspected SARS-CoV-2 infection prior to the onset of GBS. A meta-analysis by Palaiodimou et al.[284] reported that the incidence of GBS among COVID-19 patients is higher than in noninfected individuals in both contemporary and historical data. The same conclusion was drawn by Filosto et al.[285] based on a comparison of GBS incidence in 14 hospitals in Northern Italy during the years preceding the COVID-19 pandemic with data during the pandemic, from March 2020 to March 2021. Both studies[284,285] concluded that GBS tends to be more severe among COVID-19 patients compared to cases not related to COVID-19, and there is a predominance of demyelinating forms of the disease in COVID-19-related cases. They also indicated, as did Aladawi et al.[283] and Rahimi,[286] that the majority of patients with COVID-19-related GBS do not have antiganglioside antibodies. In a systematic review, including 436 patients who developed COVID-19-related GBS, Pimentel et al. described clinical and laboratory findings.[287] The mean age of patients was 61 years. Additionally, a distinct predominance of men (67.2%) was found. The clinical symptoms of COVID-19-related GBS did not differ from the cases of GBS caused by other factors, with general weakness and weakness of both upper and lower limbs being the most prominent symptom. The laboratory findings were also similar to those found in patients with GBS of other causes with typical protein-cytological dissociation in cerebrospinal fluid. The low incidence of antiganglioside antibodies in COVID-19-related GBS was also corroborated in this review. Although these antibodies play an important role in the diagnosis of GBS, the mechanism leading to demyelination and impairment of nerves is complex and involves both the complement system and immune cells. T lymphocytes and macrophages can infiltrate nerves from neural veins and reside in very close contact with myelin. Due to molecular mimicry, T lymphocytes activate macrophages after recognizing antigens, which subsequently release proinflammatory cytokines. This damages the myelin sheath and causes local increased vascular permeability, thus facilitating the migration of immune cells and intensification of inflammation.[288] The concept of intense macrophage stimulation resulting in a release of proinflammatory cytokines during COVID-19 was proposed by McGonagle et al.[289] This process, together with endothelial injury, may play an important role in damaging nerves and causing the resulting GBS symptoms in COVID-19 patients without the presence of typical autoantibodies.[290]

Autoimmunity Following Vaccination

In 2020, 2 mRNA vaccines against SARS-CoV-2 were authorized by the U.S. Food and Drug Administration for use in adults.[25] In the following year, permission was extended to younger individuals and to other vaccines based on adenovirus vectors and recombinant proteins.[25] All of these vaccines, whether based on mRNA, replicating or nonreplicating viral vectors, or S protein subunits, were designed to induce a humoral response against the SARS-CoV-2 S protein. According to “Our World in Data,” the nonprofit organization based in the United Kingdom that gathers information from official sources worldwide, by August 20, 2023, 70.5% (5620,582,121 individuals) of the world’s population had received at least 1 dose of a COVID-19 vaccine, and 64.8% (5168,306,076 individuals) had received the full vaccination protocol.[291] Universal vaccination has played an important role in reducing the number of severe cases of COVID-19, which require hospitalization and intensive treatment, thus improving survival rates.[292,293] Vaccination against SARS-CoV-2 may, however, lead to the development of

various adverse effects. Common side effects include headache, temporary pyrexia, and muscle pain, particularly at the site of injection,[294] as well as less common autoimmune-mediated events. In a review by Chen et al.,[295] clinical cases included vaccine-induced thrombotic thrombocytopenia (VITT), immune thrombocytopenic purpura (ITP), autoimmune hepatitis (AIH), GBS, IgA nephropathy, rheumatoid arthritis, endocrinological diseases including Grave's disease and diabetes mellitus type 1, and SLE. Most of these conditions were related to mRNA vaccines, although VITT and SLE were also described in patients who had received adenovirus vector-based vaccines. Among the reported VITT cases, antibodies against platelet factor 4 (PF4) were found despite the patients having had no previous exposure to any type of heparin.[296,297] ITP was reported in several distinct cases in adults who had received courses of different vaccines. A report by Simpson et al.[298] described an association between adenovirus-based vaccines and a small increased risk of developing ITP and thromboembolic events. On the contrary, no link between these phenomena and the mRNA-based vaccine had been reported. Jara et al.[299] described reports of adverse autoimmune effects of vaccination against COVID-19 in a review with a total number of 36 participants. Among neurologic, rheumatologic, endocrinologic, and hematologic diseases associated with different vaccines, the most numerous belong to the neurologic domain: GBS (10 participants vaccinated mostly with an adenovirus vector vaccine), optical neuromyelitis (5 participants vaccinated with different vaccines), and transverse myelitis (4 participants vaccinated mostly with an adenovirus vector vaccine) were the most common. Other conditions in individual cases included autoimmune encephalitis, Kawasaki vasculitis, ANCA-associated vasculitis, Graves' disease, thyroiditis, and VITT. There are also reports[300-303] describing cases of adult-onset Still's disease (AOSD) as a complication after vaccination in patients who had not been previously diagnosed with this disease. Additionally, other reports[304,305] describe COVID-19 vaccination as a potential factor causing new flares of AOSD in patients previously diagnosed and treated for this condition. A rich review was given by Camacho-Domínguez et al.[306] The report included 34 case reports documenting the development of autoimmune-related diseases after exposure to different vaccines, including thrombocytopenia with thrombosis, hemolytic anemia, Graves' disease, vasculitis, hepatitis, thyroiditis, GBS, and arthritis. On the contrary a population-based study by Peng et al.[307] on a vast group of patients reports that vaccination against SARS-CoV-2, with mRNA-based inactivated virus vaccines may, in fact, play a protective role against the development of several SARS-CoV-2-induced autoimmune conditions like autoimmune arthritis, APS, and immune-mediated thrombocytopenia.

There are a number of mechanisms proposed to explain the development of autoimmune phenotypes following vaccination against COVID-19. Molecular mimicry, for example, is mutual to autoimmunity development after vaccination and an infection with SARS-CoV-2. In both cases, viral antigens presented to an immune system mimic the host's own antigens. A second explanation is the role of adjuvants, which are included in vaccines to strengthen the immune response and make it last longer. There is evidence that some adjuvants may promote the formation of inflammasomes, which in turn facilitate autoimmune mechanisms.[308] The incidence of autoimmune conditions triggered by COVID-19 vaccines is difficult to establish as there are no reliable worldwide registers documenting these phenomena. Furthermore, distinguishing between autoimmunity caused by vaccines and flares of pre-existing autoimmunity is very difficult. Nevertheless, Jara et al.[299] concluded that the incidence of these adverse effects seems to be very low, and they should not discourage people from being vaccinated, as the expected benefits outweigh the risks of these side effects.

Pre-Existing Autoimmunity and COVID-19

The impact of pre-existing autoimmunity on the severity of COVID-19 has been widely described. However, it is important to make a distinction between testing positive for ANA and suffering from autoimmune systemic disease. In the first case, the presence of ANA is considered to be an autoimmune phenotype, which may potentially lead to the development of autoimmune disease in the future. In contrast, a diagnosis of a particular systemic autoimmune disease is based on serologic patterns and clinical symptoms, followed by immunosuppressive therapy. Additionally, systemic autoimmune diseases can provoke significant damage to vital organs such as the kidneys, lungs, and heart. This may have an influence on COVID-19 severity and outcome. For this reason, this probable influence should be considered separately for these 2 groups of patients. There are studies describing the incidence of ANA among COVID-19 patients.[249,309-315] They present results that indicate that ANA incidence in COVID-19 individuals is high. Gazzaruso et al.[309] and Chang et al.[310] tested 45 and 47 patients with SARS-CoV-2-related pneumonia for ANA, respectively. There was a high prevalence in the groups (35.6% and 21.3%, respectively). Furthermore, Gazzaruso et al.[309] estimated the incidence of LA to be 11.1% in the study group. The lack of a control group is a limitation of these findings, therefore, the relationship between ANA presence and COVID-19 outcome requires further investigation. Pascolini et al.[249] performed a study including 33 COVID-19 patients and 25 individuals with pneumonia not related to COVID-19. The authors found that 11% of patients were positive for ANA compared to 8% in the non-COVID-19 group. The prevalence of COVID-19 among adult and pediatric patients with autoimmune systemic diseases who have been treated with immunosuppressive drugs has been described by Michelena et al.[311] in a retrospective study of 959 participants with diagnosed rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis, axial spondylarthritis, juvenile arthritis, and systemic autoimmune diseases, and treated with disease-modifying antirheumatic drugs (DMARDs) including anti-TNF-alpha inhibitors, and IL-1, IL-6, and IL-17 inhibitors. The authors did not report a higher risk of contracting COVID-19 nor of having a more severe disease outcome compared to the general population. There were similar findings in the pediatric population only Filocamo et al.[312] collected data from 123 participants who had been diagnosed with rheumatic diseases and treated with DMARDs. No participant developed a severe form of COVID-19, and there had been no need to withdraw immunosuppressive therapy for any child. However, a definitive conclusion regarding COVID-19 incidence in this specific group could not be made due to the lack of a control group. A prospective study by Haberman et al.[313] included patients with COVID-19 and autoimmune inflammatory diseases treated with DMARD therapy based on anticytokine drugs. They found that the use of these medications in the treatment of rheumatic and inflammatory diseases did not worsen the outcomes of COVID-19. Similar conclusions about the safety of DMARDs in COVID-19 were reached by Monti et al.[314] and Favalli et al.[315]

Management of Long COVID and Future Perspectives

At the start of the COVID-19 pandemic the main task was to limit the spread of the virus and deliver treatment for a constantly increasing number of infected individuals. Over time the long-lasting consequences of COVID-19 have become an important factor affecting the lives of many convalescents and therefore there is a need for preventive measures and appropriate treatment to overcome them. According to the review by Koc et al.[53] the approach to that has been divided into 3 parts: prevention of infection, treatment of acute phase of the disease and finally management of long-COVID symptoms. Prevention is based on a healthy lifestyle (balanced diet, physical activity, good sleeping habits), which is important in reducing comorbidity and maintaining the proper activity of the immune system, personal protection (wearing face masks, social distancing, washing hands) to decrease the risk of infection, and finally vaccination to reduce the risk of severe course of the disease and the development of long COVID. The treatment of acute COVID-19 is important in diminishing inflammation and therefore reducing tissue damage and consequently the risk of the development of long-term side effects, including autoimmunity. The third part is focused on in-

dividuals who have developed long COVID. All convalescents require clinical assessment to detect those who present conditions related to past SARS-CoV-2 infection. The diagnosis and treatment of long COVID may require the involvement of different specialties to cover as many clinical presentations of long COVID as possible. An approach to establishing treatment based on either identifying symptoms or interfering in the mechanisms responsible for long-COVID development (for example: hypercoagulability, neuroinflammation, development of autoimmunity) is described in the review by Davis et al.[316] However, the authors emphasize the fact that the described treatment options are based on either trials performed on small groups of patients, or on knowledge and experience gained from treating similar conditions. According to the authors extensive research and education of medical professionals are needed to counteract the long-lasting effects of the COVID-19 pandemic.

Summary

SARS-CoV-2 has spread worldwide and infected hundreds of millions of individuals. It is regularly developing novel mutations resulting in the emergence of new variants with increased virulence and transmissibility, and as such, will likely remain circulating in the human population as a pathogen of great importance. The recent pandemic showed that COVID-19 is not a simple respiratory tract infection but, in many cases, develops into a systemic disease affecting vital organs and causing long-lasting health deterioration. Due to the large number of infected individuals, convalescents, and those at risk of infection, delayed COVID-19-related conditions are presenting challenges to healthcare systems and social care in many countries. Among a broad spectrum of diseases and symptoms reported in convalescents we focused on several specific conditions with autoimmune backgrounds. In all of them there is a connection between the virus and the host's immune response with subsequent hyperinflammation, endothelial injury, and development of autoimmunity. The first 2 processes are very well described, whereas the relationship between autoimmunity and COVID-19 is still not fully understood. Although the link between other viral infections and autoimmunity has been well studied and described, it is still unclear if SARS-CoV-2 is able to independently induce the development of autoimmunity or whether this process requires additional triggers. The growing volume of published data delivers descriptions of a broad collection of different autoimmune-related diseases diagnosed in COVID-19 convalescents, but cannot fully explain the contribution of SARS-CoV-2 to the development of autoimmunity. In many cases, there is no available information about patients' health status, especially pre-existing autoimmunity prior to the COVID-19 onset. Furthermore, defining autoimmunity itself is difficult. The group of conditions with an autoimmune background is heterogeneous: there are both systemic and organ-specific autoimmune diseases, and subsequent categories within these 2 groups include different risk factors, immunological mechanisms, and various diagnostic approaches. Although an increasing amount of data suggests that infection with SARS-CoV-2 leads to the development of a variety of autoantibodies against a broad spectrum of host antigens, the clinical implication of these phenomena still needs to be established. The presence of autoantibodies without clinical symptoms is usually not sufficient to make a diagnosis of an autoimmune disorder. On the other hand, there is a possibility of developing autoimmune conditions due to past SARS-CoV-2 infection without the presence of specific autoantibodies, as was described for COVID-19 convalescents with Guillain-Barré syndrome. Another conundrum is the observation that although COVID-19 generally results in an increased antiphospholipid antibodies prevalence, these antibodies are not necessarily associated with disease severity or risk of thrombosis. This shows that the testing for antiphospholipid autoantibodies alone may not be a sufficient assessment of the risk of thrombosis after recovery from COVID-19. All these factors make attempts at establishing and explaining the true nature of the relationship between COVID-19 and autoimmunity a challenging task. This, however, should be done to provide better healthcare and treatment to huge number of patients with COVID-19-associated autoimmunity in the future. Some lessons may be learned from autoimmunity induced by anti-SARS-CoV-2 vaccination, especially regarding the specific molecular features of the virus, which play an important role in inducing autoimmunity. This may be an important matter in the future as the number of vaccinated people is high and is expected to grow at various rates worldwide. As a result, so is the number of possible autoimmune conditions related to the vaccination. Along with the large number of COVID-19 convalescents, as time goes by, there will be an increase in the number of people affected by complications, including those with backgrounds of autoimmune disease. This will pose new challenges for healthcare systems and professionals around the world.

There are some limitations of our narrative review. First of all, our work covers a very broad subject hence some of its aspects are only discussed in general and others may not be addressed. Additionally, some of the information that we decided to include in this review comes from case reports and trials on small groups and thus the objectivity of our work is limited. Finally, we are fully aware that our literature search may not be complete due to the ever-increasing amount of scientific literature on the subject.

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.

CRediT authorship contribution statement

Paweł Kozłowski: Conceptualization, Investigation, Methodology, Formal analysis, Writing – original draft, Software, Visualization, Validation. **Aleksandra Leszczyńska:** Investigation, Data curation, Visualization. **Olga Ciepiela:** Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing, Validation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2024.100068.

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