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Review Article

SARS-CoV-2: Mapping its features that made it as a unique virus

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ABSTRACT: SARS-CoV-2 has attracted the attention of nearly the whole world during the last four years. It is a Corona virus that is responsible for the deaths of millions. It is responsible for economic corruption in many countries. As a response, excessive vaccination programs were installed everywhere. But many variants are elevated, and the virus proves its ability to escape from the immune system because of different mutations. The progress in different scientific domains—instrumentation, bioinformatics, and the like—makes fast vaccine development easier. As a response, new strategies were introduced, including new vaccine production and administration strategies, genomic surveillance, immunopeptidome, gene sequencing, and the like, to enable the vaccine to cover all the targeted populations at the correct time and to install an early alarm system against any elevated new variants. This review contains more information about some important stations in the history of vaccine development and the strategies invented by scientists to control different viruses and other microbes. Some important issues that might influence the type of vaccine used for SARS-CoV-2 are addressed. They include their symptoms, the virus evasion of the innate immune system, the response of adaptive immunity, and the like. Although the world still needs to better understand the SARS-CoV-2 behavior to win the war against it, previous historical successful vaccine productions, important examples, and stations during the human struggle against the viruses are described and discussed.

KEYWORDS: epitopes; control strategies; immunopeptidome; vaccine; variant; SARS-CoV-2

1. Introduction

It is wiser to cut the virus transmission cycle rather than treat it. Wild animals are the most reclaimed ones. Signs of humans' awareness about disease transitions could be traced in our everyday practices, legends, history, folk memory, different activities, observations, experiences, knowledge, practices, and the like. For example, the criteria used to classify the animal species of concern for SARS-CoV-2 epidemiology was the ability to shed infectious virus and to transmit SARS-CoV-2 to other individuals. Evidence of animals that could transfer SARS-CoV-2 includes the American mink (*Neogale vison*), raccoon dog (*Nyctereutes procyonoides*), cat (*Felis catus*), Syrian hamster (*Mesocricetus auratus*), ferret (*Mustela furo*), house mouse (*Mus musculus*, for some virus variants only), Egyptian fruit bat (*Rousettus aegyptiacus*), deer mouse species (*Peromyscus spp.*, not present in Europe), and white-tailed deer (*Odocoileus virginianus*)[1]. Keeping away from wild animals will help cut the cycle of unusual viruses like those that have started to attack humans in the last few decades. Unusual viruses could also be transmitted from wild animals to domesticated ones. Historically, wild beasts were domesticated (such as cats and dogs)

to protect against other wild ones (such as rats, foxes, and wolves). During their everyday computation/activities, dangerous microbes start to come to our backyard. To avoid such a mix, some beliefs and practices of some ethnic groups describe orders that include eating any kind of meat! In terms of other inhabited carnivores or beasts, which have nails, it is not clear yet why wild beasts transfer dangerous diseases, but domesticated ones did not, but only after sudden attack or contact with wild animals. That might be because of long-term historical adaptation and contacts between humans and domestic animals. Meanwhile, in current years, this stability has proved to be a fable. Farmers and companies active in the business of animal farming should put animals' protection against any contact with wild animals as one major safety concern.

Farm animals usually do not transmit serious illnesses; even viruses such as smallpox (cows), sheep pox (sheep), and chicken pox (chickenpox) are not fatal to us. In contrast, they could protect us against our own specific viruses, such as the seriously fatal virus, the smallpox. Apparently, lay people have a concise and correct image of this perception (such as the story of the milkmaid and Edward Jenner). Our modern lifestyle kept us away from domesticated animals and from some wild animals (such as the zoo). Did we miss those free chances for protection? Be closer to the wild animals. And the like.

One important activation is the nonpharmaceutical interventions for managing SARS-CoV-2. Such activities include face masks, hand hygiene, respiratory etiquette, surface and object cleaning, ventilation, UV light, humidity, contact tracing and quarantine, rapid antigen testing, school closures, travel-related measures, staying at home, and the like[2]. Meanwhile, the viruses are usually able to bypass the first defense line, which keeps them away from us at the correct natural distances. For that, during our historical straggles against pathogens, including viruses, human talent invents some amazing protection strategies such as variolation (more details blow), herbal treatment, patients' isolation, and the like. But, in some cases, the community becomes susceptible. An epidemic strike is an example. But epidemics usually happen after a large rest period, which does not mean that the virus did not infect at all. But infect at levels less than the epidemic level. That is a sign of the presence of either herd immunity or other specific conditions that enable viruses and other pathogens to attack us at levels that could be given the name "sub-Epidemic".

How do communities interact with illness? Particularly after the epidemic has disappeared! Measles could be given as an example. The old art starts when a child (gaining infection) has symptoms like measles. His mother is telling other mothers, and they are all gathering their children (those who did not gain measles before) in one place to gain the infection and address them with red clothes. Science proves that the measles virus (and some other viruses) could be more fatal for adults, but not for children! Sometimes strong immune systems, like adults' immune systems, could cause serious side effects, such as cytokine storms in the case of SARS-CoV-1 and, in particular, some variants of SARS-CoV-2 or for patients with health problems. Should we follow this concept? Did our chilled (non-vaccinated) become immunized as well by using such a simple practice? Today, the image is completely different, and many do not like to experience such successful old practices. Nerveless, scientists are invited to reinvestigate any of them and re-modulate them to be more acceptable to modern communities. Anyhow, such practices are still running here and there and have not completely disappeared. Keeping any previous successful experiences running and stopping pushing a force to replace them with modern technology might be useful in critical cases or places where there is no possibility to use modern technology (e.g., vaccines) or there is not enough capacity to use modern technology for everyone.

The two famous historical pandemic viruses are smallpox, which infects Native Americans (unknown death number), and Spanish influenza (50 million deaths in 1918). The Greek historian

Herodotus, born 484 BC, documented that every Babylonian was an amateur physician since it was custom to lay sick in the street so that anyone passing by might offer advice[3,4]. Thucydides (430 BC) describes plague in Athens (over 100,000 deaths in 430 BC); "only those who had recovered from the plague could nurse the sick because they could not contract the disease a second time[5]. In the past, pandemic areas were isolated. No one enters it. Few know that one should also not leave his place for another. Other famous documented events include *Yersinia pestis* (50 million deaths in 1340). Humans were always searching for information, tools, ideas, advice, and the like that could help them, particularly to enable them to be healthy and satisfy the different demands of other lives.

Earlier, when specifying viruses using a microscope, philosophers and thinkers such as Pasteur's emphasis that virulence is not a constant attribute but a variable property. A property that can be lost and later recovered. Virulence could be decreased, but Pasteur suspected that it could rise as well. He believed that rising virulence was what gave rise to epidemics[6]. Successfully, smallpox and rinderpest were nearly eradicated, and many of the human viruses were under control. Meanwhile, in the last decade's conversion. Other viruses start to attack us with new infections caused by novel, uncommon virus species. For example, HIV (40 million deaths in 1980–2000), H1N1 "Swine Flu" (300,000 deaths in 2009), Zika, Ebola, Severe Acute Respiratory Syndrome (SARS), Middle East respiratory syndrome (MERS)" and SARS-CoV-2 "COVID-19". Did we change our lifestyle? Which factor(s)/activity could be claimed? This review concerns collecting some evidence and highlighting some odd responses (such as immunocompromised patients, children, precedents, patients with SNPs in particular gene(s), and the like).

One should not neglect the efforts made by scientific institutions, companies, organizations (such as the World Health Organization (WHO)/FAO), politicians, decision-makers, and the like to establish a global safe system to control the existing pandemic(s)/epidemic(s) or prevent the expected coming ones. Also, the community's fast responses to instructions given by experts have a good impact on controlling some issues. Nerveless, the lifestyle, economic activities, and social behaviors of our world are still being stuck by this pandemic[7].

The world reaches some acceptable level of collaboration. Meanwhile, the warning from a newly elevated infection in different parts of the world is still alarming. The world should install a better strategy for prevention, protection, and treatment. And questions should always be given the correct attention. For example, why do viruses attack and re-attack us? And what could we do?

This review deals with

1) Mapping critical stations in human history concerning viruses, immunity, and vaccine development and production.
2) Giving the essential information about the SARS-CoV-2 virus, symptoms, immune system reactions, the different personal responses, the important molecular aspects, and the like.
3) Summarizing different tactics, strategies, and how scientists found solutions might help many and even open a new window for controlling SARS-CoV-2 and the other viruses. An idea that might not be useful for one person or in a certain place might be useful for others where they might still need time to be compatible with the standard codes.
4) Describing different vaccines prepared by different strategies, including old (viable, attenuated, inactivated, antibodies, and the like) and new (RNA, DNA, protein, peptide vaccines, etc.).
5) Describing important strategies (immunopeptidome, personalized treatment, virus ghost, etc.) that could help in controlling viruses in general and SARS-CoV-2 as the hottest issue. One could not forget

that a simple strategy could save some countries from antibiotic resistance by simply keeping some antibiotics out of the pharmacy and enabling their use only in hospitals (in emergence cases). Other ideas or concepts might be extracted from nonspecific, similar experiences as well.

2. Corona virus

There are two genera in the Coronaviridae family: coronavirus and torovirus. Coronaviruses are enveloped, 120–160 nm particles with an unsegmented genome of a positive-sense single-stranded RNA (infectious) (26–e32 kb)[8]. The helical nucleocapsid is 9–11 nm in diameter. SARS-CoV-2 can largely be transmitted through contact, particle transition, airborne, fecal-oral, blood-borne, mother-to-infant, animal-to-animals, and animal-to-human (Hossain et al. 2020). The virus enters the human body through the mucosa of the nose and oropharynx, and some gets deposited in the lungs. Beside the lungs, other organs express angiotensin-converting enzyme 2 (ACE2) receptors on the surface of cells, such as the heart, kidneys, and intestines[9,10]. The viral genome (29.8 kp) consists of 14 open reading frames (ORFs), which encode 27 proteins. Two-thirds of the viral RNA is translated into two large polyproteins. In SARS-CoV and MERS-CoV, two polyproteins, pp1a and pp1ab, are processed into 16 nonstructural proteins (nsp1–nsp16), which form a viral replica transcriptase complex. Those nsps rearrange membranes originating from the rough endoplasmic reticulum (RER) into double-membrane vesicles, where viral replication and transcription occur[11,12]. The other ORFs of SARS-CoV-2 on one-third of the genome encode four principal structural proteins: spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins, as well as several accessory proteins with unknown functions that do not participate in viral replication.

2.1. The status of the current pandemic, SARS-CoV-2

The SARS-CoV-2 emergence in 2019 is causing an ongoing COVID-19 pandemic. For example, on 31 August 2022, >600 million COVID-19 patients, and 6.5 million deaths were reported globally[13,14].

2.2. Evasion strategies

Coronaviruses (CoVs) have advanced evasion strategies to bypass host defense and increase replication and transmission[15–19]. SARS-CoV-2 can evade the first innate immune responses. This could happen by dropping IFN levels. Patients are genetically and physically different. Mild and moderate COVID-19 patients have in their serum low levels of IFN types I and III[17,19]. The IFN type I and III production are reduced at the post-transcriptional levels. SARS-CoV-2 inhibits the release of mRNA from transcription sites and/or triggers degrading transcripts in the nucleus[17,19]. SARS-CoV-2 also encodes additional proteins that disrupt RLR sensing pathways, signaling, or effector functions. SARS-CoV-2 ORF9b, N, and M proteins can inhibit the expression of IFN-β and proinflammatory cytokines. It does that by interfering with the RIG-I and MDA5 pathways. ORF9b is also capable of blocking the TLR3-TRIF pathway[16,19–22]. Moreover, SARS-CoV-2 nonstructural proteins also contribute to host immune evasion[13]. There are other mechanisms involved in evasion of the innate immune system, such as mutating the target site(s).

2.3. SARS-CoV-2 entry

Entry receptors

COVID-19 can affect almost any organ[23–26]. The virus protein S is a fusion glycoprotein. It was divided into two functionally distinct parts (S1 and S2)[27–29]. SARA-CoV-2 can bind to the endothelial layer through angiotensin-converting enzyme 2 (ACE 2) receptors expressed on target cells. The S protein

is responsible for receptor-binding and determines host range and cell tropism[11]. The S proteins of various coronaviruses interact with a wide range of receptors, including ACE2, dipeptidyl peptidase 4, aminopeptidase-N, and sialic acid moieties, to facilitate the entry process. This diversity of receptor use may help explain the strong potential for zoonotic transmission of coronaviruses to humans[30]. SARS-CoV-2, like SARS-CoV, uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells, with its main co-receptor being transmembrane protease serine 2 (TMPRSS2)[9,10,31–42]. This large protein comprises a short C-terminal tail located inside the virion, a transmembrane domain, a rod-like S2 domain responsible for the fusion process, and a large globular S1 domain, within which RBD is located. In advance of interaction with entry receptors, the virus binds to adhesion receptors. This concentrates the virus on the cell surface. Next, the virus binds to entry receptors, which initiates a fusion of viral and cellular membranes. Finally, viral nucleoproteins enter the cytoplasm. The internalization site depends on the availability of proteases needed to trigger the transformation of the S protein into a fusogenic state. *In vitro* models show that human coronaviruses use an endocytic entry pathway in which gradual acidification of the microenvironment activates endosomal cathepsin B (catB) and cathepsin L (catL), which effectively prime S protein and begin entries[43,44]. Other studies showed that human coronaviruses bypass this process and use serine proteases (transmembrane protease serine 2 [TMPRSS2], kallikrein 13) present on the cell surface. In such cases, fusion occurs on the cell surface, and endocytosis is not need[9,42,45–50].

Furin (the cleaving SARS-CoV-2 spike protein) and CD147 (basigin) have arisen as possible viral entry facilitators[41,51–55]. Three C-type lectin receptors, CD169 (Siglec-1, Sialoadhesin), CD209 (DC-SIGN), and CD299 [LSIGN, DC-SIGNR, C-type lectin domain family four-member M (CLEC4M)], enhance ACE2-dependent viral entry in their role as attachment receptors[56–60]. CD169 is a surface molecule expressed in macrophages at several anatomical sites that mainly promote adhesion to neutrophils, and was described as an entry mediator for retroviruses[61]. CD209 was proposed to act as a receptor on liver sinusoidal endothelial cells[62]. Lectin proteins were shown to activate the complement system[63] and stir further inflammatory responses by beginning cytokine production in myeloid cells[64], which fits well into the established concept of inflammasome activation by SARS-CoV-2[65]. Neuropilin-1 (NRP-1), originally described as a pro-angiogenic protein and a mediator for neuronal cell guidance in the developing nervous system[66], was shown to potentiate viral transmission of SARS-CoV-2[38,39,67]. Kringle containing transmembrane protein 1 (KREMEN1) and asialo-glycoprotein receptor 1 (ASGR1) as 'receptor-like host factors' in SARS-CoV-2 were proposed[68,69]. Both proteins are described as acting independently from ACE2. Although KREMEN1 is a known entry receptor for several enteroviruses, such as coxsackievirus A10[70,71]. Alternative viral entry molecules, monocytes, and (alveolar) macrophages were described as possible vector cells for SARS-CoV-2 entry and transmission[72–77]. Viral replication in AMs and viral uptake were also shown in mouse models using transcriptomic profiling[72,76] A cellular shift towards proinflammatory monocytes was described in alveoli[78]. SARS-CoV-2 uses M1 macrophages with their distinct proinflammatory cytokine profile as a vehicle for transmission and infection of the alveolar epithelium[72,79]. Ingesting of SARS-CoV-2 in monocytes elicits a strong inflammatory response[80,81], which is critical in COVID-19. Bräutigam et al.[82] discussed the role of 10 possible viral entry molecules, ACE2, TMPRSS2, furin, CD147, CD169, CD209, CD299, NRP-1, ASGR1, and KREMEN1, and addressed their clinical relevance and anatomical distribution[82]. Bräutigam et al.[83] show that SARS-CoV-2 N-protein is detectable in AMs expressing ACE2 and other entry receptors and suggest an important role for AMs as a cellular hub for entry and transmission of SARS-CoV-2[83]. Although the lungs are the SARS-CoV-2 target organ, 2% of cells in this tissue are ACE2

positive. Nerveless, ACE2-positive cells are extensively found in the small intestine, gallbladder, kidneys, testes, thyroid, adipose tissue, heart muscle, vagina, breast, ovary, and pancreas[9,24,25,27,84,85].

3. Symptoms of COVID-19

The symptoms of COVID-19 could be used as a rapid diagnostic tool. They are variable, ranging from mild symptoms to fatal illnesses. Meanwhile, they can be categorized into three common groups of symptoms that were identified.

- Group 1, where patients developed a cough, sputum, shortness of breath, and
- Group 2, where patients developed a musculoskeletal symptom cluster with muscle and joint pain, headaches, and fatigue.
- Group 3, where patients developed a cluster of digestive symptoms with abdominal pain, vomiting, and diarrhea.

Common symptoms include coughing, fever, loss of smell (anosmia), taste (ageusia), headaches, nasal congestion and runny nose, muscle pain, sore throat, diarrhea, eye irritation, and toes swelling or turning purple. In moderate-to-severe cases, they cause breathing difficulties. At least a third of people who are infected with the virus do not develop noticeable symptoms at any point in time[86,87]. The same strains show less severity. For example, an Omicron variant in the U.S. since December 2021 has less severe symptoms compared with other variants[88]. Meanwhile, SARS-CoV-2 dissimilar variants with diverse severity were identified.

4. SARS-CoV-2 variants

Mutations at the N-terminus and receptor-binding region, including p.Glu484Lys, are found in the most dangerous variants[89]. Dissimilar variants, including those from the UK, South Africa, India, California, and Brazil, have appeared. Delta variant is more virulent and speedily spread[90]. The variants of concern (VOC) include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). Meanwhile, Delta and Omicron are the most alarming ones[89]. In 2022, a new variant with Delta backbone and Omicron spike has arisen[91]. The SARS-CoV-2 virus is highly mutated[92]. Omicron itself has >100 subvariants at present, among which BA.1 (21K), BA.2 (21L), BA.4 (22A), BA.5 (22B), and BA.2.12.1 (22C) are dominant ones[93]. The Omicron variant has a high risk of immune evasion[94,95]. The multiple mutations encompassing epsilon variant demonstrate the independent convergent changes in SARS-CoV-2, with its spike protein mutation L452R in Delta (L452R), Kappa (L452R), and Lambda (L452Q) being present[96]. To control such un-normal circumstances, administering a third booster dose is motivated after the emergence of the B.1.617.2 (delta) variant throughout the world. Third doses of the vaccines mRNA1273, BNT162b2, AZD1222, and Coronavac prompted a spike in levels of neutralizing antibodies when administered several months after the second dose. These decreases in vaccine-induced antibody levels reflect a decline in protection against the virus[97].

5. SARS-CoV-2 during the infection process

SARS-CoV-2 affects different important organs, but the most important one is the lung. A few minutes without oxygen can result in death or brain deterioration[98]. SARS-CoV-2 could show no symptoms until it becomes well adapted in infected people's cells. For that, asymptomatic individuals speedily spread the virus[90,99,100].

Some other properties involved in its pathogenicity could be summarized in the following points:

1) Its entry and replication modes in cells during the infection/cell defense mechanism cause severe reactions.
2) In the lungs, their various activities as well as the activity of the immune system (both cellular and humoral immune responses) and any existing co-infection interfere with the respiration process. SARS-CoV-2 replication in airway epithelia needs motile cilia and microvillar reprogramming[101].
3) The fast virus promotors utilize the energy and power of the lung cells because of the virus's fast replication.
4) The time between the correct response of the adaptive immune system and its adaptation of lung cells is enough to put the immune system against the fact that a virus is already invading the cells.
5) Innate pathways are dysregulated in some individuals during SARS-CoV-2 infection.
6) Various related cell death pathways exist, including robust NETosis or PANoptosis.
7) T cells are also affected by the SARS-CoV-2 infection.

5.1. Cytokine storms and ROS

Some viruses cause a localized, exaggerated response, resulting in the secretion of high levels of cytokines. There is some evidence that the SARS epidemic of 1993 may have caused similar, unregulated immune cell cytokine secretion[102].

Sars-CoV-2 as being a new virus, did not experience before by our immune system, it will be capable of bypass innate defenses and reach to lung cells even to the immune cells. Our first defense line is the innate immune system, which includes type I, type II, and type III interferon signaling cascades and interferon-induced genes. They are playing a role in limiting viral entry, translation, replication, and assembly and accelerating the development of adaptive immunity by providing co-stimulatory signals and upregulating the expression of important proteins (for example, MHC antigens). While few specific interferon-stimulated genes (ISGs) were documented to have direct antiviral activity against SARS-CoV-2, some were described, including ISG15, which augments MDA5 signaling after recognizing SARS-CoV-2 viral RNA[103], and LY6E, which appears to block fusion and entry of coronaviruses into cells. Larger-scale genetic screens evaluated the effect of human ISGs on SARS-CoV-2 replication[104].

Excessive innate immune activation could lead to systemic inflammation and severe disease. Thus, a balance must be achieved that speedily restricts SARS-CoV-2 infection without resulting in excessive inflammation and tissue injury. NK (natural killer) cells have antiviral activity against SARS-CoV-2 but become functionally impaired in severe COVID-19[105].

The variable innate immune response of healthy people can be genetically confirmed by the TLR receptor. Sepsis patients with SNPs of TLR1 hypermorphic variants have an association with a heightened susceptibility to organ dysfunction, death, and gram-positive bacteremia infection[106]. TLR4 is the major receptor for lipopolysaccharide (LPS). Variants of TLR4 can make individuals susceptible to sepsis. Genome-wide association studies (GWAS) have linked TLR4 polymorphisms to pathogen susceptibility and disease severity[107]. Plasma cytokines should be monitored dynamically to assess the degree of the cytokine storm. SARS-CoV-2 might induce excessive and prolonged cytokine responses, resulting in lung damage and multiple organ failure (MOF). A violent cytokine storm causing immune pathological damage may be a real "killer" in critically ill patients.

Pathogenic mechanism of inflammatory cytokines, derived from IMM and neutrophils[108]. Therapeutic approaches to manage the COVID-19 cytokine storm decrease COVID-19-associated morbidity and mortality[109]. The SARS-CoV-2 spike induces autophagy through the intracellular ROS-suppressed PI3K/AKT/mTOR axis, which then leads to inflammatory responses and apoptosis in

infected cells. Anti-inflammatory drugs are not effective and remain unclear)[110]. It is difficult to illuminate the separate roles of pyroptosis in COVID-19, which include inflammasomes and caspases[111]. Managing its pathogenesis through specific cytokine storm checkpoints can reduce mortality[112]. The cytokines produced from COVID-19 infections have also contributed to the elevation in the number of T-cells in asthmatic patients[113].

5.2. Bacterial-SARS-CoV-2 associated-co-infections

Identifying and treating other respiratory pathogens is important[114]. Bacterial co-infections play additional pathogenic roles[115]. Diverse individuals have diverse bacterial co-infection[116]. Co-infecting pathogens are important in any treatment strategies[117,118]. SARS-CoV-2 infection is associated with a distinct shift in the composition of the nasal microbiome, including *P. aeruginosa* and *B. cepacian*[119]. *P. aeruginosa* is capable of producing alginate and expressing the T6SS gene[120].

5.3. Viral co-infection

Fage et al.[121] highlighted that SARS-CoV-2 existing with other viruses (that infect the respiratory organ) could help in its control[121]. Influenza a(h1n1)pdm09 virus but not respiratory syncytial virus could interfere with SARS-CoV-2 replication during sequential infections in human nasal epithelial cells. According to Fage et al.[121] the mechanism involved in the viral interference is mediated by producing interferon[121].

5.4. Cell death during the infection

Proteases play important roles in SARS-CoV-2 infection and replication. Various cell death pathways exist, including robust NETosis or PANoptosis. Parallel inhibition of NLRP3 assembly along with gasdermin D oligomerization increases the therapeutic effect of caspase-1 inhibition to prevent pyroptosis[122]. Necrosis, including necroptosis and pyroptosis, is the predominant form of alveolar epithelial cell death in COVID-19-induced patients. The DAMPs released from necrotic alveolar epithelial cells are potential drivers of progressive alveolar tissue damage in COVID-19[123]. The related neuronal damage in the URT leads to anosmia[111,119]. β-Coronaviruses can be hypothesized to maintain cell death pathways. The role of ORF3a in inducing the extrinsic pathway similarly to SARS-CoV infection should be deepened. T cells are also affected by the SARS-CoV-2 infection. SARS-CoV-2 triggers inflammatory responses and cell death through caspase-8 activation[124]. Molecules such as c-FLIP, NF-kB inhibitors, or caspase-8 activators could be included among the drugs used to contrast COVID-19. Fast and direct approaches to targeting the uncontrolled response of the immune system after the infection could involve using molecules to inhibit the action of TNF and IFN-γ. SARS-CoV-2 infection triggers several cell death pathways that could become pharmacological targets[125].

Age, gender and personal immunity

Personal genetics play a role in determining susceptibility to COVID-19. Patients are not uniformly responsive to complement-targeting therapies. SNPs (single nucleotide polymorphisms) in complement and coagulation pathways underlie the genetic predisposition towards severe COVID-19 disease in some patients. Interferons or other immune mediators can drive differential susceptibility[126–128]. Patients with autoantibodies account for up to 10% of hospitalizations for severe COVID-19 and 20% of deaths[129,130]. Anti-interferon antibodies are present in a small fraction of critically ill patients, especially in men.

Age, male gender, and some pre-existing conditions, such as severe asthma, are associated with worse COVID-19 outcomes, including death. Gender and age are responsible for changes in myeloid cell populations, which are a feature of severe COVID-19[131]. A higher myeloid-derived suppressor cell

(MDSC) count in patients with COVID-19 correlates with reduced transcription of cytokines by peripheral monocytes[132]. Defective DC migration to the lymph nodes and the reduced priming of T cells in older mice are reported because of their increased expression of prostaglandin D2 (PGD2). A PGD2 antagonist protected older mice from disease[133]. MS1' cells are risen in patients with severe COVID-19. These cells are thought to be immunosuppressive and may contribute to the reduction in T cell populations that was seen in severe COVID-19. Cystic fibrosis (CF) patients with poorer lung function and post-transplant status are at higher risk for worse clinical outcomes in coronavirus disease[134].

Elderly people with weak immune systems and people with autoimmune diseases were the most vulnerable to contracting the virus[116,135]. Gender and age can be associated with specific uncontrolled inflammatory immune responses, which drive aggressive inflammation, hyper-cytokinemia, and the wide organotropism of SARS-CoV-2 collateral tissue damage and systemic failure[136,137]. That could be related to imbalanced ACE/ANGII/AT1R and ACE2/ANG(1–7)/MASR axes signaling[138].

6. Global SARS-CoV-2 genomic surveillance

Because of the elevation of new variants after excessive vaccination programs, it becomes clear that there is a need for installing a system that can monitor any new elevated variant to be identified on the spot. That enables better control and better distribution of the data, which could enable the fast production of new vaccines specific to this variant. For example, Saifi et al.[139] have conducted a study on SARS-CoV-2 VOCs, mutational diversity, and clinical outcomes[139]. They find significant mutations, T4685A, N4992N, and G5063S in the RdRp; T19R in the NTD spike; and K444N and N532H in the RBD spike region, to be associated with the Delta mortality patients. Mutations T19I in the NTD spike, Q493R and N440K in the RBD spike, G18C, and R413S in the nucleocapsid gene were significantly associated with the Omicron mortality patients. The docking studies of Remdesivir with mutant viral proteins, including Nsp12, Nsp13, and the spike RBD region, demonstrated a reduction in the binding strength of Remdesivir to mutant spike proteins for both mortality groups. Their findings suggested the possible role of these mutations in reduced drug efficacy and a possible role in the progression of disease severity[139]. Emerging SARS-CoV-2 VOCs cause an impending global crisis[140].

In fact, none of the new vaccine production strategies based on the virus genome and structure/function will work without the virus genome sequence. Meanwhile, the first SARS-CoV-2 genomes were shared on 10 January 2020[24,25,141]. The United Kingdom established the COVID-19 Genomics UK Consortium (COG-UK). The U.S. government invested US$1.7 billion to expand genomic capacity for COVID-19[141,142]. In Australia, an integrated public health genomics surveillance system is being developed (AusTrakka)[143]. Another genomic surveillance system was built up in South Africa[141,144]. Puerto Rico installs its own[145]. In Italy, over 20,000 viral genomes have been sequenced since the start of the pandemic[146].

This permitted:

1) Identify new viral variants[146].
2) Detecting circulating viral diversity.
3) Identifying epidemiologically linked individuals.
4) Identifying national and international transmission routes.
5) Enables bioinformatics and knowledge resources to detect emerging VOC prior to their international expansion.
6) Large-scale models with relatively sparse sampling were used[141,147,148].

The CDC summarizes the importance of a comprehensive system for SARS-CoV-2 genetic surveillance in three points[149]:

1) Mutations (nucleotide substitutions) occur in viruses and accumulate with continued viral spread; these mutations result in variants that may have dissimilar attributes. Genomic surveillance identifies circulating variants to speedily inform public health response efforts[149].
2) Testing, treatment, and vaccination programs can be improved based on regularly updated surveillance of variants, including updating forthcoming vaccines if needed[149].
3) Detecting variants that are more transmissible or cause more severe disease supports outbreak preparedness, prevention efforts and strengthens the public health response[149].

Several other studies report the importance of genomic analysis in controlling the epidemic of SARS-CoV-2[150]. Integrated genomic surveillance enables the tracing of person-to-person SARS-CoV-2 transmission chains[151]. For genomic surveillance of SARS-CoV-2, the ECDC recommends two complementary sampling approaches[152]:

- Representative sampling of SARS-CoV-2 RT-PCR positive cases from existing, population-based surveillance systems[152];
- Targeted sampling of SARS-CoV-2 positive cases occurring in special settings or populations[152].

Bhat et al. (2021)[153] reported that VOCs and VOIs provide a framework for closely monitoring the low-frequency mutations for their forthcoming functional importance in transmission and immune escape[153]. These methods offer novel means to detect variants that are phenotypically or antigenically diverse[154]. Genomic surveillance will facilitate greater early anticipation[154]. Improved SARS-CoV-2 sequencing surveillance permits identifying new variants and signatures in infected patients[147]. SARS-CoV-2 shows a complicated relationship among virus antigenicity, transmission and virulence[155]. Predicting and cataloging VOCs prior to their emergence would enable the preemptive design of therapeutics and public health measures to be employed when needed[156].

7. Immunopeptidome

The epitope profiling of RBD-based antigens in SARS-CoV-2 revealed the critical antigenic determinants. It includes three immunodominant epitopes. They are a conserved epitope (350VYAWN354) exposed on the surface of the viral spike protein trimer; a variable epitope among diverse virus strains (473YQAGSTP479) found in the receptor-binding motif (RBM); and a conserved cryptic cross-reactive epitope (407VRQIAP412) shared by the RBD of SARS-CoV-2 and SARS-CoV[157].

These data can elucidate humoral immune responses to the spike protein's RBD. That will enable the development of new vaccines[158]. SARS-CoV-2 mutated epitopes can erode adaptive immunity. Identified epitopes in the COVID-19 mRNA vaccine are important. They can be used as a basis for studying immune escape, viral variants, the design of the vaccine, and therapy. Mutation panel assays for VOCs' epitopes induced by the mRNA vaccine are rich in breadth. VOC can grant resistance against viral evolutionary escapes in the future. That represents an advantage of vaccine-induced immunity[158]. Human leukocytes' antigens class I epitopes (HLA-I) and class II epitopes (HLA-II) were identified. They were used for immunopeptidomes. Epitopes are mostly canonical and out-of-frame peptides derived from spike and nucleocapsid proteins. The epitopes of the membrane proteins come in at the second level[159].

In cito antigens are proteolytically processed into peptides. The peptides were then presented on the surface of infected cells by human MHC. MHC, known as HLA molecules, presented the peptides to T[160]. This peptidome of HLA represents an immunological signature. The circulating cytotoxic T cells

($CD4^+$ and $CD8^+$ T cells) can recognize it through their T cell receptor (TCR). It causes clearance and lysis in infected cells, catalyzing immune responses[161]. Different indigenous populations express distinctive and unique HLA profiles. That varies from other ethnic groups' profiles[162]. Exploring the SARS-CoV-2-derived HLA peptide repertoire enables characterizing the viral epitopes. These specific epitopes can activate cytotoxic T cells. B cells recognize external viral epitopes. T cells can be elicited by all viral proteins. That includes several canonical and non-canonical viral ORFs[20]. Bioinformatics prediction for the binding affinity of HLA-I and HLA-II was employed to detect the epitopes of SARS-CoV-2[163–169]. The data are based on the reactivity assays and biochemical binding assays (IMMUNITRACK)[164,167,169–171].

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Conflict of interest

The author declares no conflict of interest.

Abbreviations

CF	cystic fibrosis
GWAS	genome-wide association studies
HDCV	human diploid cell vaccine
SG	interferon-stimulated genes
MDSC	myeloid-derived suppressor cells
MERS	Middle East respiratory syndrome
MOF	multiple organ failure
MV	measles virus
MVA	modified vaccinia Ankara
NDV	Newcastle disease virus
NK	Natural killer
ORF	Open reading frames
PBMC	Peripheral blood mononuclear cells
PCEC	purified chick embryo cell culture
PVRV	purified vero cell rabies vaccine
RBD	receptor-binding domain
RBM	receptor-binding motif
RER	rough endoplasmic reticulum
SARS	severe acute respiratory syndrome
SNP	single nucleotide polymorphisms
TCR	T cell receptor
VOC	variants of concern
VSV	vesicular stomatitis virus
WHO	World Health Organization

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