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REVIEW

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Immuno-epidemiology and pathophysiology of coronavirus disease 2019 (COVID-19)

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Abstract

Occasional zoonotic viral attacks on immunologically naive populations result in massive death tolls that are capable of threatening human survival. Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the infectious agent that causes coronavirus disease (COVID-19), has spread from its epicenter in Wuhan China to all parts of the globe. Real-time mapping of new infections across the globe has revealed that variable transmission patterns and pathogenicity are associated with differences in SARS-CoV-2 lineages, clades, and strains. Thus, we reviewed how changes in the SARS-CoV-2 genome and its structural architecture affect viral replication, immune evasion, and transmission within different human populations. We also looked at which immune dominant regions of SARS-CoV-2 and other coronaviruses are recognized by Major Histocompatibility Complex (MHC)/Human Leukocyte Antigens (HLA) genes and how this could impact on subsequent disease pathogenesis. Efforts were also placed on understanding immunological changes that occur when exposed individuals either remain asymptomatic or fail to control the virus and later develop systemic complications. Published autopsy studies that reveal alterations in the lung immune microenvironment, morphological, and pathological changes are also explored within the context of the review. Understanding the true correlates of protection and determining how constant virus evolution impacts on host-pathogen interactions could help identify which populations are at high risk and later inform future vaccine and therapeutic interventions.

Keywords SARS-COV-2 · COVID-19 · MHC · HLA · Virus evolution · Pathogenesis

Introduction

In this twenty-first century, the resurgence of novel, lethal, and highly contagious zoonotic viruses to which there is no pre-existing immunity pose a great threat to the survival of mankind as described in Table 1[1–3]. The evolutionary

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"arms race" between the host and the pathogen surges on and reaches its crescendo when the infectious agent mutates so quickly to successfully evade the host's immune system [4]. This leads to a disease outbreak which could later develop into a pandemic as massive deaths soon ensue. This is followed by the global incapacitation of social, health, economic, and government systems [5–7]. If measures are not put in place to curtail spread of infection, these new emerging biological threats could serve as a catalyst for the total extinction of the human species [8]. Case in point in 1918, a new strain of H1N1 influenza viruses termed the "Spanish flu" led to the deadliest pandemic in human history [9]. This virus infected roughly one-third of the world's population and caused an estimated 50 million deaths worldwide [10].

More recently, novel strains of the usually benign coronaviruses, that routinely cause harmless common colds and have low virulence [11], mutated from their natural reservoir hosts and transitioned towards causing excess infectivity and mortality in humans. Notably, in 2002, Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1)

Table 1 List of zoonotic contagious viruses that cause lethal infections in humans (Source: cdc.gov and ncbi.nlm.nih.gov).

Virus	Genome (size) sense	Disease	Host	Source of transmission	Symptoms
Avian influenza A	ssRNA (13.5 kb)-negative	Bird flu	Chicken, ducks, geese	Respiratory droplets/dust	Fever, cough, and sore throat
Swine origin influenza virus (S-OIV)	ssRNA (13.5 kb)-negative	Swine flu	Pigs	Respiratory droplets/dust	Fever, cough, and lethargy
West Nile virus (WNV)	ssRNA (10.9 kb)-positive	West Nile fever (WNF)	Birds	Mosquito bite	Fever, encephalitis, and meningitis
Ebola virus	ssRNA (18.9 kb)-negative	Ebola virus disease (EBD)	Bats, non-human primates	Body fluids, tissues, infected fruit bats, and non-human primates	Fever, fatigue, and diarrhea
Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	ssRNA (29.7 kb)-positive	Severe Acute Respiratory Syndrome (SARS)_	Bats, civet cats	Respiratory droplets	High fever, pneumonia, and diarrhea
Middle East respiratory Syndrome Coronavirus (MERS-CoV)	ssRNA (30.1 kb)-positive	Middle East respiratory Syndrome (MERS)	Dromedary camels	Respiratory droplets	High fever, pneumonia, and diarrhea
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)	ssRNA (29.9 kb)-positive	Coronavirus disease 2019 (COVID-19)	Not determined	Respiratory droplets	High fever, pneumonia

ssRNA, single-stranded ribonucleic acid; *kb*, kilobase

originated from the Guangdong province in Southern China and was rapidly spread to greater than 8,000 people in over 25 different countries [12]. As a result, over 750 deaths have been observed internationally and a case fatality rate of over 15% reported in certain populations [13–15]. In 2012, another coronavirus termed Middle East Respiratory Syndrome Coronavirus (MERS-CoV) mutated and jumped the species barrier from camels to humans. This led to infections in 2,496 individuals with 868 (35%) documented fatalities [16]. However, MERS infection events remain localized within the Middle East due to the fact that disease spread relies on a single camel to human vertical transmission event [17].

In December 2019, a third newly emerged coronavirus later named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was detected in Wuhan, the capital city of the Hubei province in China [18]. Following this, SARS-CoV-2 rapidly spread globally with over 17.8 million cases being reported globally on August 1, 2020, accompanied by over 684,096 deaths [19]. In the early stages of the SARS-CoV-2 epidemic in Wuhan, way before any public health interventions had been implemented, the pandemic potential of the virus was evaluated based on its basic reproduction number (R0). The R0 of SARS-CoV-2 was estimated as 3 to 4 implying that each infected case transmitted the virus to roughly 3 to 4 new individuals with doubling occurring every 5 days [20]. Similarly, Sanche et al. estimated the R0 to be likely as high as 5.7 [21], while Li et al. documented an R0 of 2.38 (95%

credible interval (CI): 2.03−2.77) [22]. Following the spread of SARS-CoV-2 to different parts of China, the effective reproduction number (Re) was calculated after the implementation of public health interventions such as city lockdowns, social distancing, and quarantine to mitigate the spread of the virus. All these efforts were undertaken to reduce the R0 to less than 1 in order to eliminate the possibility of a pandemic [23]. The Re was later estimated as 0.98 (95% CI: 0.83–1.16) during the period of 24 January–8 February thus highlighting the role of different public health strategies in reducing the global spread of SARS-CoV-2 [22].

Virus evolution due to changes in genomic structure and epidemiology

Although SARS-CoV-2 has a lower-case fatality rate (currently estimated at 2–4% as of April 2020 and peaking as high as 10% in highly populated areas such as New York [24]), far greater deaths have been reported within a short time span in comparison with SARS-CoV-1 and MERS-CoV [25]. This could partly be attributed to the fact that SARS-CoV-2, which has been shown to have close to over 80% and 50% sequence homology with SARS-CoV-1 and MERS-CoV respectively [26–28], acquired critical mutations within its genome. This observed difference in genetic composition could possibly favor enhanced infectivity in target cells and accelerate

disease pathogenesis. Recently, up to 93 mutations have been observed in the entire genome of SARS-CoV-2 with a variable number (6 to 11) of open reading frames (ORF) reported from different geographical regions [29]. Notably, two-thirds of the viral RNA is housed within the first ORF (ORF1a/b) where translation of the two viral polyproteins pp1a and pp1ab together with 16 non-structural proteins (NSP) occurs (21). It has been reported that within SARS-CoV-2 non-structural protein 2 (NSP2), positive selection pressure facilitated a mutation at amino acid position 321 from an apolar amino acid in in the Bat SARS-like coronavirus to glutamine. This amino acid substitution confers the ability to form stable hydrogen bonds within this endosome-associated protein that could speculatively result in enhanced viral pathogenesis [30].

The other third of the viral genome comprises ORFs that encode structural and accessory proteins together with the E, M, S, and N genes that translate envelope (E), matrix (M), spike surface glycoproteins (S), and nucleocapsid (N) structural proteins [31]. Sequence alignments also revealed several mutations within the spike surface glycoprotein in the receptor-binding domain (RDB), which could affect the ability of the virus to attach to the human receptor angiotensin converting enzyme 2 (ACE2). These changes enable SARS-CoV-2 to have a higher binding affinity to human, cat, and ferret ACE2 receptors in comparison with SARS-CoV-1 [18]. Lastly, at the junction of the S1 and S2 subunits of the S protein, SARS-CoV-2 has unique insertions of a polybasic cleavage site (RRAR). This could facilitate effective cleavage by proteases and could modulate virus infectivity. However, the functional roles of RRAR are yet to be fully understood [32].

Intriguingly, the insertion of similar cleavage sites into the junction of S1 and S2 subunits of SARS-CoV-1 has been shown to augment cell to cell fusion [33]. Furthermore, the addition of proline residues to the RRAR cleavage of SARS-CoV-2 sites favors the addition of O-linked glycans which could shield critical epitopes of the SARS-CoV-2 spike protein from immune system recognition [34]. Random mutations allow RNA viruses to cross species barriers and adapt to conducive host-pathogen interactions that will maximize viral replication and transmission while minimizing harm to the host [35, 36]. Current SARS-CoV-2 mutations have led to lineage changes from the original strain that was first detected in Wuhan, China. These SARS-CoV-2 lineages were classified as L (new) and S (ancestral) based on changes in amino acid 84 located in ORF8 whose role in the viral life cycle remains unknown. It was observed that though these lineages coexist concurrently, the L lineage has gradually become highly prevalent in comparison with the S lineage [37]. However, studies are yet to be performed to test whether lineage differences are accompanied with changes in fitness and viral pathogenesis.

Real-time tracking of SARS-CoV-2 reveals that current circulating strains have now spread to all populations across the globe including the Icelandic people [38]. To track the day-to-day evolution of the virus, scientists are encouraged to submit viral sequences to publicly available databases like GISAID (https://www.gisaid.org/CoV2020/) where virus divergence from the original strain from Wuhan is analyzed in real time using the nextstrain platform (https://nextstrain.org/ncov/global) [39]. Based on phylogenetic analysis, three central variants (A, B, and C) were classified based on differences in amino acids. As of 4 March 2020, variant A and C were predominantly found outside East Asia, while variant B was predominantly localized within East Asia, perhaps indicating that this variant is immunologically or environmentally adapted to this region.

Sub-clusters, or clades, of A have a unique mutation at nucleotide position T2905C but which encodes a synonymous amino acid with the ancestral genome linked to 4 Chinese individuals from Guangdong who carried the ancestral genome. B variants differ from A by two-point mutations (the mutation at nucleotide position T8782C resulting in a synonymous mutation, and a mutation at nucleotide position C28144T resulting in the non-synonymous mutation from a leucine to a serine) [40]. Our nextstrain analysis carried out on 2 May 2020 revealed that the greatest diversity of publicly reported SARS-CoV-2 clades was reported in the Asian continent. Radial phylogenetic trees distanced by time indicate that the predominant clade in Asia and the USA was A2a, while Africa was largely populated with the A2 clade. Europe offered a different visual perspective as the A3 clade was found to be the most common (Fig. 1).

The implications of viral evolution as evidenced by differences in clades acquired as the virus propagates across new host niches on viral pathogenesis are yet to be fully understood. However, a recent report argues that despite social distancing, the differences in deaths observed in the West Coast versus the East Coast of the USA could be driven by clade-associated mutations of the SARS-CoV-2 spike glycoprotein (31). The B1 clade which predominates the west coast has an aspartic acid (D) at codon 614 of the S protein while the A2a clade on the east coast possesses a glycine (G) at the same position. Phylogenetic analysis shows that the substitution mutation D614G occurred from shifts from the ancestral D residue [41]. It remains hypothesized that this mutation affects a critical region of the heavily glycosylated spike which could account for differences in virulence, viral fusion, and accompanied mortality [42].

Virus structure and replication

When visualized under an electron microscope, the 3-dimensional (3D) appearance of SARS-CoV-2 appears pleomorphic (round or oval) and has a helical nucleocapsid together with spiky protrusions emanating from its surface that give
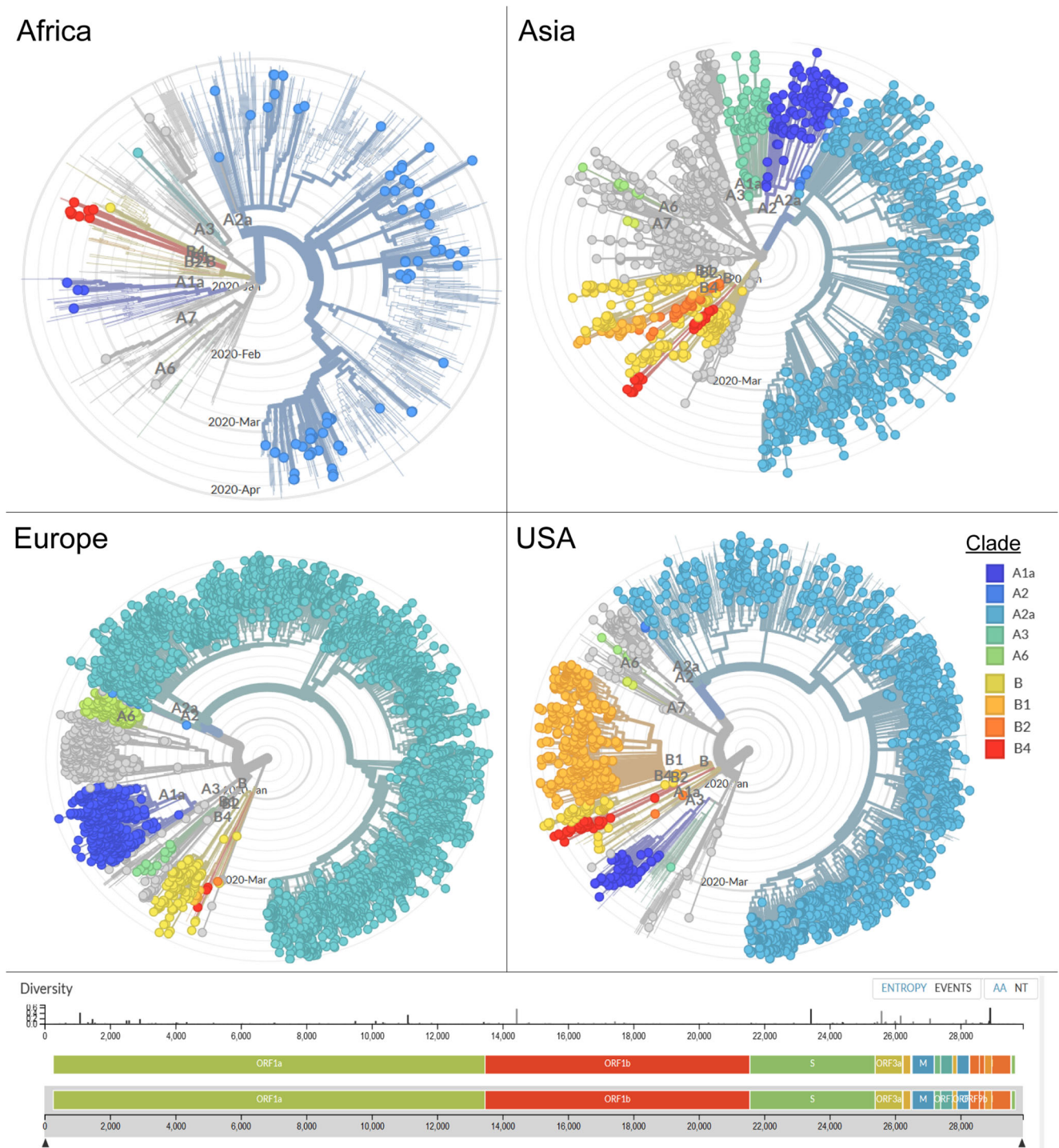
Fig. 1 Phylogenetic analysis of full-length SARS-CoV-2 sequences submitted to Global Initiative on Sharing all Influenza Data (GISAID), (https://www.gisaid.org/CoV2020/). Radial phylogenetic trees were generated using Nextstrain (https://nextstrain.org/ncov) after the SARS-CoV-2 global dataset was filtered according to Africa, Asia, Europe, and the USA regions. The branch lengths are distanced by time and individual points colored by Clades (A1a, A2, A2a, A3, A6, B, B1, B2, and B4) with Wuhan-Hu-1/2019 used as a reference. Analysis was carried out on 2 May 2020

it a crown-like appearance [43]. The viral structure comprises an envelope comprising three structural proteins (S, M, and E) that encases a single-stranded positive sense 30 kilobase (kb) genome [44] coupled with the structural protein N [45, 46]

(Fig. 2). The S protein is heterotrimeric and projects out of the outer layers of the virus [47, 48], while the N protein binds to RNA to form the nucleocapsid and directs the viral replication cycle. The M protein is the most structurally abundant and is

crucial to providing shape and stability to the virus. The E protein is usually least expressed but is critical to maturation of the virus [49, 50]. As a result of its intricate structure, SARS-CoV-2 has been found to be a relatively stable virus with the ability to survive outside the host for prolonged periods of time. It has been documented to survive up to 3 h in aerosols [51].

Intriguingly, the virus persisted for 24 h on cardboard and 2 to 3 days on plastic and stainless steel without any signs of observed decay [52]. Hence, when COVID-19 patients were admitted to a biocontainment unit and in hospital settings, it was documented that besides aerosol transmission, SARS-CoV-2 could be shed and indirectly spread through contamination of objects within the environment like personal items, toiletries, and room surfaces [53, 54]. Upon inhalation of SARS-CoV-2, the S1 subunit of the S protein through its RDB domain attaches to the ACE2 receptor expressed on epithelial cells (goblet/secretory cells and ciliated cells) at high density [55] and type II pneumocytes in the lower respiratory tract of humans [56]. ACE2 is also widely distributed in different cells of diverse tissues and organs ranging from the gastrointestinal tract, cardiovascular, urogenital, and central nervous systems [57, 58]. This accounts for the wide tissue dissemination of SARS-CoV-2, observed in COVID-19 patients, which arises from the availability of several target cells that further propagate infection following inability to resolve lung infection [59].

The attachment of the virus to host target cells could be prevented by pre-existing neutralizing antibodies or cross reacting antibodies from earlier related infections such as SARS-CoV-1 that specifically attach to the SARS-CoV-2 highly variable RDB domain of the S1 subunit [45, 46]. Post attachment, the cellular serine protease termed as the cell surface–associated transmembrane protease serine 2 (TMPRSS2) cleaves the S protein into S1 and S2 [60]. This separation activates the fusion of the viral envelope with the host cell resulting in the release of the viral nucleocapsid into the cytoplasm [61]. Upon deposition of the viral genome into the host cell, direct translation of ORF1a/b genes begins resulting in the generation of polyproteins pp1a and pp1ab that are further processed to form non-structural proteins [62].

These non-structural proteins form interconnected double membrane replication transcription complexes (RTC) in which subgenomic RNAs are encoded to generate accessory and structural proteins [63, 64]. These replication compartments help concentrate viral and host transcription factors and offer a "safe haven" for protection of the virus from the hosts' exonucleases and other host innate immune responses [65]. The newly generated genomic RNA, nucleocapsid proteins, and envelope glycoproteins then navigate and traverse the endoplasmic reticulum and Golgi network where they

Fig. 2 Key structural proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that include the spike surface glycoprotein (S), membrane protein (M), RNA attached to nucleocapsid protein (N) and envelope protein (E).
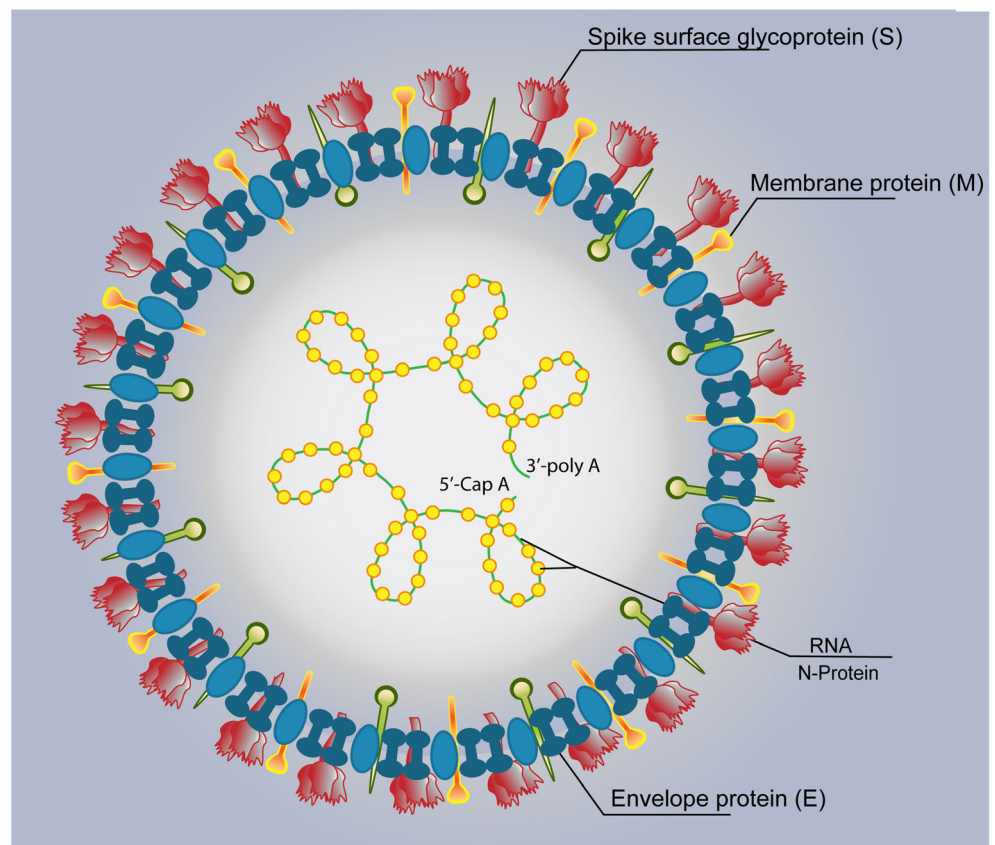
assemble and form viral particles which later fuse with the plasma membrane and hijack the lipid bi-layer to form progeny viral particles [66].

To maximize viral replication, coronaviruses utilize a pathogenic factor, non-structural protein 1 (nsp1), which promotes the endonucleolytic cleavage of the hosts RNA and blocks the translation any remaining host RNA. This takeover of the host genomic machinery ensures maximum generation of viral progeny at the expense of the host's needs [66, 67]. In addition, nsp1 inhibits the host expression of type 1 interferons thus offering a milieu that favors virus replication [68]. This is attributed to the fact that these cytokines favors optimal stimulation of T cell responses by enhancing antigen presentation through increased expression of major histocompatibility complex 1 (MHC 1) on various cells [69]. Similarly, the highly conserved nsp16 facilitates enhanced virus replication by facilitating virus evasion from recognition from the hosts pattern recognition receptor (PRR) melanoma differentiation-associated protein 5 (MDA5) and as a result downregulates the type 1 interferon response [70]. Comprehensive proteomic analysis of SARS-CoV-2 revealed that SARS-CoV-2 proteins such as Orf6 and nsp13 also target the host interferon signaling pathways. Orf3a and NSP9 of SARS-CoV-2 also antagonize host E3 ubiquitin ligases that lead to the dysregulation of host antiviral signaling [71–73].

Host genetics: influence of HLA alleles on susceptibility and resistance to SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infections

During viral infections, effective antiviral immunity is fostered through cooperative interactions between the host's specific innate and adaptive immune responses. Antigen-presenting cells recognize and process viral antigens into smaller peptides that are later attached onto major histocompatibility complex (MHC) class I/II molecules or Human Leukocyte Antigen (HLA) alleles [74]. Specific peptide and HLA combinations are then recognized by T cells (CD4 T cells and CD8+/ cytotoxic T cells (CTLs)) of the adaptive immune system. This leads to the respective CD4+ T cell orchestration of overall immune cell function through cytokine secretion and CTL killing/ clearance of virus-infected cells.

The interaction of T cell receptors (TCRs) with a unique specific set of HLAs determines the efficacy to induce SARS-CoV-2 specific immune responses that may confer protection or predispose the host to infection [75, 76]. SARS-CoV-1 structural proteins such as S, M, and N are more immunogenic in comparison with NSPs. SARS-CoV-1 N protein's 219 to 235 residues comprise HLA-A*0201 restricted epitopes [77, 78]. Position 331 to 365 residues also consist of HLA-A*2402

restricted CTL epitopes that are capable of inducing memory T cell responses [79–81]. Notably, HLA-Cw1502 and DR0301 confer resistance to SARS-CoV-1 infection [82]. Alternatively, MHC class I HLA-B*-4601, HLA-B*-0703, HLA-Cw* 0801 and MHC class II HLA-DRB1*1202 have previously been associated with increased susceptibility to SARS-CoV-1 [83–85], while MHC class II HLA-DRB1*11:01 and DQB1*02:02 have been found to exacerbate susceptibility to MERS-CoV [86].

Recently, Nguyen et al. conducted an elaborate in silico analysis of the binding affinities between SARS-CoV-2 peptides and various MHC class I molecules that spanned 145 HLA-A, -B, and -C genotypes. They predicted that HLA-B*46:01 bound to a fewer number of viral peptide antigens and as a result postulated that individuals who lack this allele have an increased risk of vulnerability to SARS-CoV2 infection. On the other hand, HLA-B*15:03 bound to a large number of SARS-CoV-2 peptides that were highly conserved within various human coronaviruses and as such were hypothesized to induce cross-protective T cell–based immunity [87]. Interestingly, Grifoni and Kiyotani et al. also reported extensive B cell and T cell epitope sequence similarity between SARS-CoV-2 and SARS-CoV-1 [26, 88]. This further emphasizes the possibility of the existence of cross-reactive protective immune responses that could be inferred from memory responses generated from earlier exposures to other related coronaviruses.

Immune evasion and subsequent disease pathogenesis

The innate immune response is the first line of defense against invading microorganisms. The host's innate immune response uses a wide variety of PRRs ranging from toll-like receptors, RIG-I like receptors such as MDA5, C-type lectin receptors (CLRs), and nucleotide binding and oligomerization domain (NOD)-like receptors to recognize a variety of highly conserved residues on SARS-CoV-2 [89]. Unsurprisingly, SARS-CoV-2 targets cells such as nasal epithelial cells found in the respiratory tract that highly express viral entry factors such as ACE2 and TMPRSS2 and are enriched with a diversity of innate immune genes [90]. Nasal epithelial cells highly express viral entry factors such as ACE2 and TMPRSS2, but are also enriched with a diversity of innate immune genes [90].

During virus attachment, SARS-CoV-2-specific or cross-neutralizing antibodies from SARS-CoV-1 [45, 91, 92] could inactivate the virus [93], prevent viral attachment to target cells [94], and perform opsonization for clearance by the complement pathway and Fc receptor–mediated phagocytosis of alveolar macrophages [95, 96]. Upon successful infection of lung epithelial cells and subsequent viral recognition, the

release of type I interferons is immediately evoked from the epithelial cells. Dendritic cells and macrophages within the lung microenvironment secrete type I interferons upon recognition of the virus through their PRRs. Collectively, this sustains a potent antiviral response by inhibiting virus replication, ensuring efficient antigen presentation of peptides to CD4^{+} and CD8^{+} T cells and efficiently promote specific adaptive T cell responses and cytotoxicity of CD8^{+} T and natural killer (NK) cells [97–100].

Recent transcriptomic data showed that robust CD8^{+} T cell responses accompanied with clonal expansion were observed in individuals who only develop mild disease symptoms and those who cleared SARS-CoV-2 from the lungs [101]. In mild and moderate cases, the clearing of COVID-19 infection has been reported to occur within 10 days following the onset of symptoms which include shortness of breath, fever, dry cough, and dyspnea [102–104]. Following this brief inflammatory phase, the alveolar macrophages clear all debris arising from apoptotic virus-infected cells, limit the buildup of surfactant, and resolve inflammation within the lung microenvironment by secreting cytokines like IL-10, transforming growth factor beta (TGF-β) and increased expression of checkpoint inhibitors such as CD200 that strive to return this niche to its conventional anti-inflammatory state [105]. Together, this ensures optimal tissue remodeling, maintenance of the lung barrier, and clearance of airways where efficient gaseous exchange is fostered within the air sacs following the brief inflammation phase [106–108], (Fig. 3).

Alternatively, the virus is capable of overpowering all barricades set up by the host immune system and later establishing successful infection within the lung microenvironment [109]. This is followed by dissemination of infection into other tissues and organs where the virus leaves a devastating trail of gross systemic pathology in its wake [110, 111]. To achieve this, SARS-CoV-2 escapes detection from any neutralization antibodies present or cross-neutralizing antibodies generated from earlier infection with SARS-CoV-1. In worst-case scenarios, SARS-CoV-1 cross-neutralizing antibodies could lead to antibody-dependent enhancement (ADE) [112]. SARS-CoV-2 non-neutralizing antibodies that bind to regions of the S protein outside the RDB domain have greater chances of generating ADE responses [113].

During ADE, antibodies attached to non-neutralized virus gain entry into macrophages through Fc receptors (FcR) and reprogram them to secrete proinflammatory cytokines that sustain viral pathogenesis [114]. SARS-CoV-2 also distorts type I IFN signaling leading to delayed secretion of type I interferons. This results in augmented virus replication which reaches its maximum 5–6 days after the onset of symptoms [115]. The immense replication of the virus within epithelial cells and enhanced virus entry into alveolar macrophages leads to increased cell death by pyroptosis as the levels of cytokines such as IL-1β and IL6 that drive the formation of the inflammasome

cascade are elevated [116, 117]. As a result, a massive loss of alveolar macrophage frequencies mirrored with an enrichment of inflammatory Ficolin-1+ (FCN1^{+}) macrophages within the lung bronchoalveolar occurs [101].

These inflammatory macrophages together with other dysregulated antigen-presenting cells (APCs) then forward processed peptides to the adaptive immune system in a defective manner that leads to impaired virus specific T cell responses. Hence, while high frequencies of T cells that secrete high levels of the TH1/ IL-17 family of cytokines that are crucial for viral eradication have been noticed [118], these cells express high levels of hyperactivated (CD38/Human Leukocyte Antigen-DR (HLA-DR)) and exhaustion markers such as the programmed death ligand 1 (PD-1)) [119]. As a result, this hyperactivated state dampens host-specific T cell responses and further impairs T cell functionality [120–122]. In addition, CD4^{+} T cells from individuals who develop severe symptoms of COVID-19 have been reported to have defective IFNγ secretion and as such poorly orchestrate help to other cell subsets [122].

Lastly, the N protein of SARS-CoV-2 binds to mannose-binding lectin (MBL) leading to the activation of the alternative complement pathway [123]. This leads to the deposition of anaphylatoxins such as C5a that serve as chemo attractants for other inflammatory cells such as monocytes, neutrophils, and eosinophils through the secretion of diverse inflammatory cytokines and chemokines [123, 124]. This partly contributes to the ongoing cytokine storm as the excessive unchecked production of cytokines such as IL-6, IL-10, GMCSF, IL-1β, and TNF-α ensues [125, 126]. This uncontrolled release of inflammatory cytokines results in both local and systemic pathology. Within the lungs, injury occurs to the lung endothelium, epithelial cells, and bronchoalveolar capillaries leading to elevated vascular permeability, disseminated intravascular coagulation, focal demarcation of hemorrhages, and proteinaceous exudates within alveolar spaces [127–129]. Shortness of breath arises from poor oxygen supply/ diffusion and low efficiency of gaseous exchange that gives the lungs an appearance of bi-lateral ground-glass opacity during computed tomography (CT) scans [130]. Systemic effects of COVID-19 also include damage to the central nervous system, which presents with acute hemorrhagic necrotizing encephalopathy [131], altered mental status, and seizures [132]. As a result of the cytokine storm, multiple organ failure that is characterized by clotting and elevated D-dimer levels within the cardiovascular system occurs. Acute kidney injury also takes place alongside necrotic destruction of the lymph nodes and spleen [133–135], (Fig. 4).
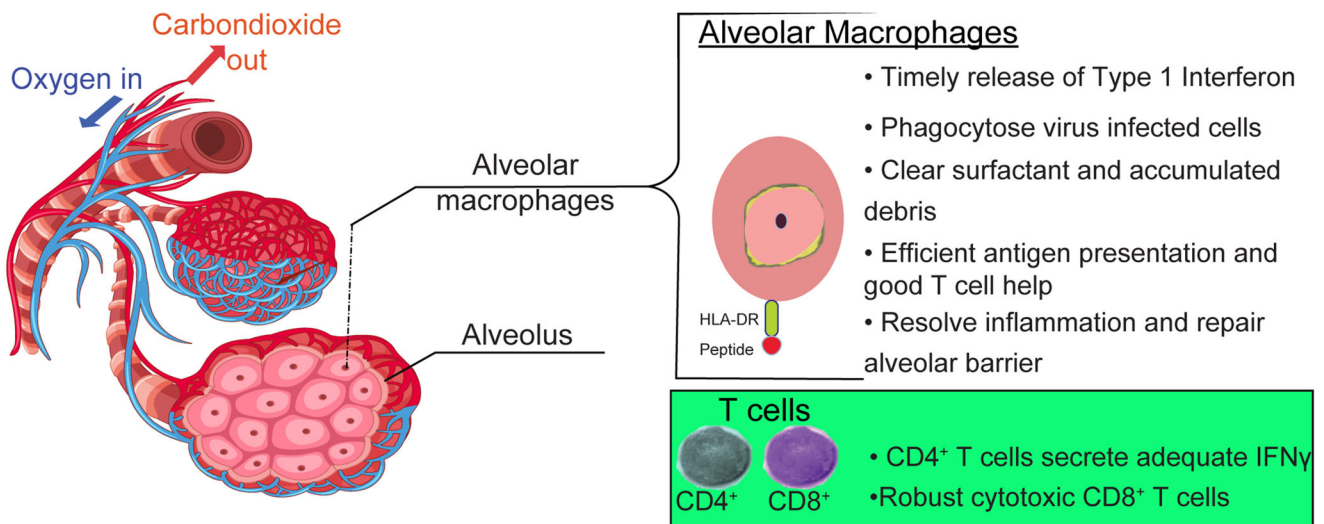
Conclusions and future perspectives

This review has focused on both virus evolution and transmission patterns, changes in virus structure that enhance

Human respiratory system
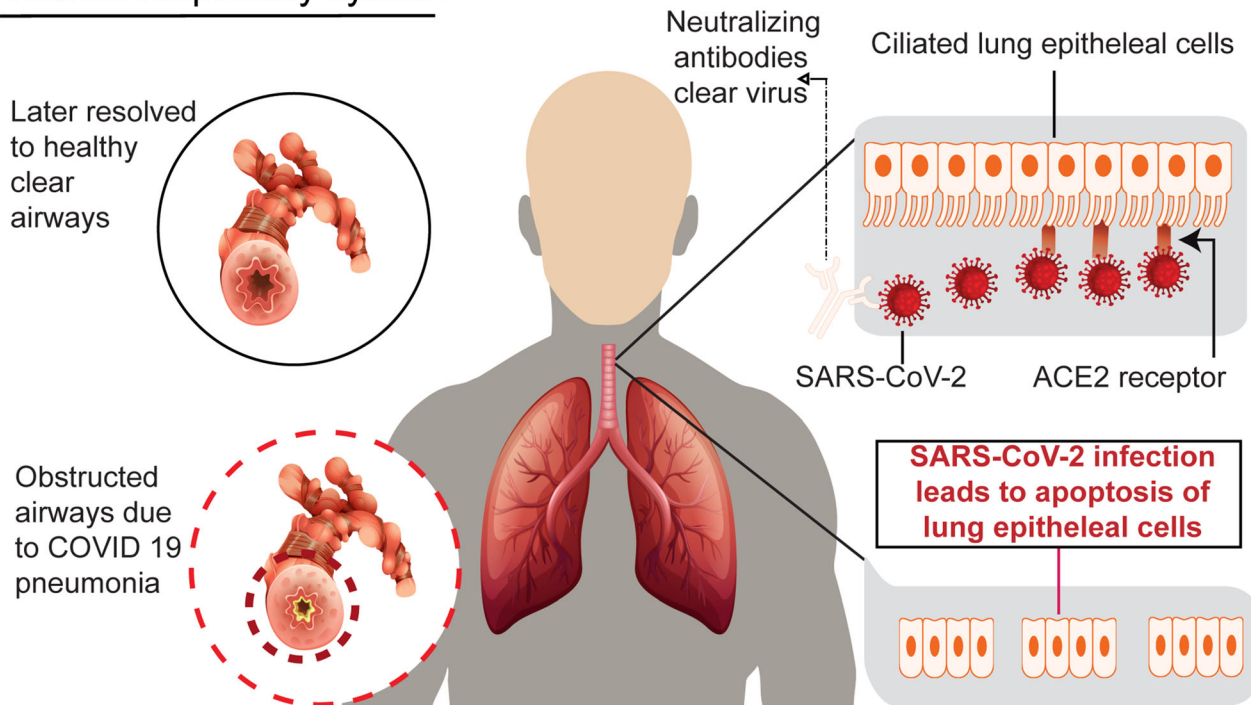
Efficient alveolus gaseous exchange

Fig. 3 Immunological events that occur in individuals who develop asymptomatic/mild to moderate symptoms of COVID-19 following exposure to SARS-CoV-2. Infection can be cleared by neutralizing antibodies (nabs). Upon recognition of foreign invaders via pattern recognition receptors (PRRs), macrophages secrete type I interferons that lead to an antiviral state. In addition, these macrophages phagocytose virus-infected cells that could have been opsonized by the nabs, carry out efficient antigen presentation to T cells, clear all the debris in the lungs, and resolve inflammation. As a result, highly functional T cells (CD4+ T cells expressing high levels of IFNγ and increased CD8+ T cell cytotoxicity) are obtained.

pathogenesis, and the immune evasion strategies that are used by the virus to evade immune detection. Except for the brief sidenote on targeting macrophages as reservoirs/carriers for SARS-CoV-2 , we chose not to delve into therapeutic options
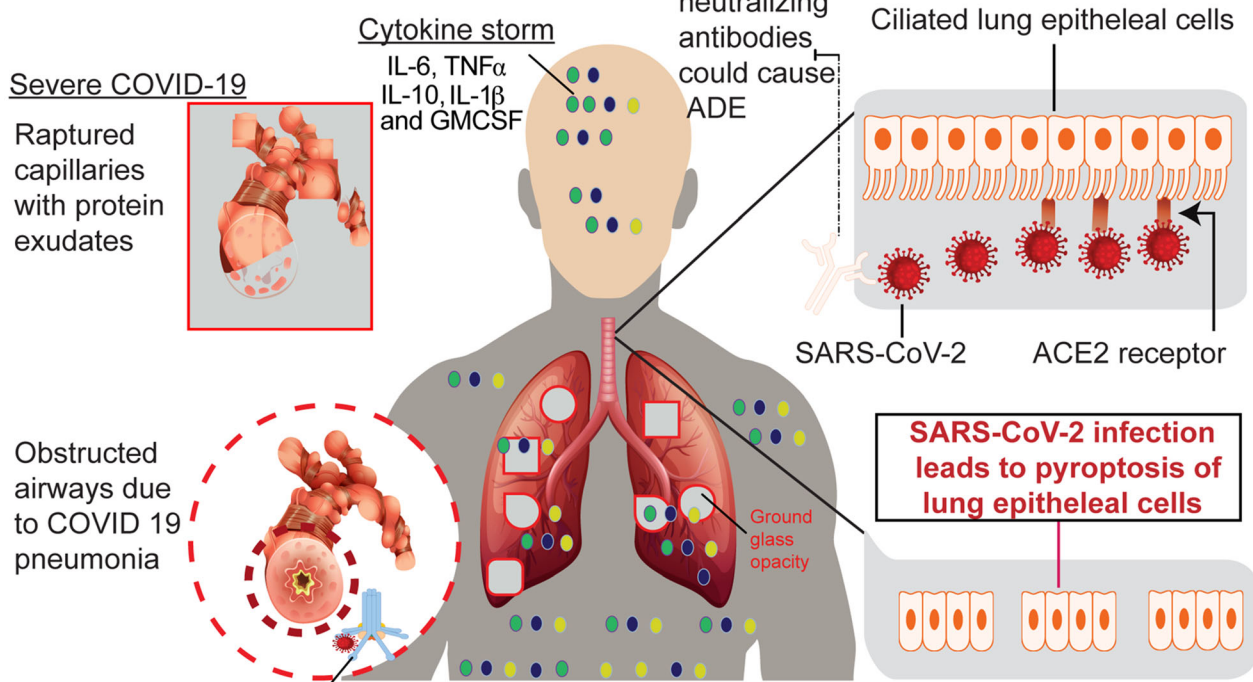
that could be utilized to eradicate the pathogen as these approaches have been elaborately discussed in separate reviews [71, 109]. Indeed, comprehensive analysis of several tissues revealed that macrophages play a crucial role in redirecting

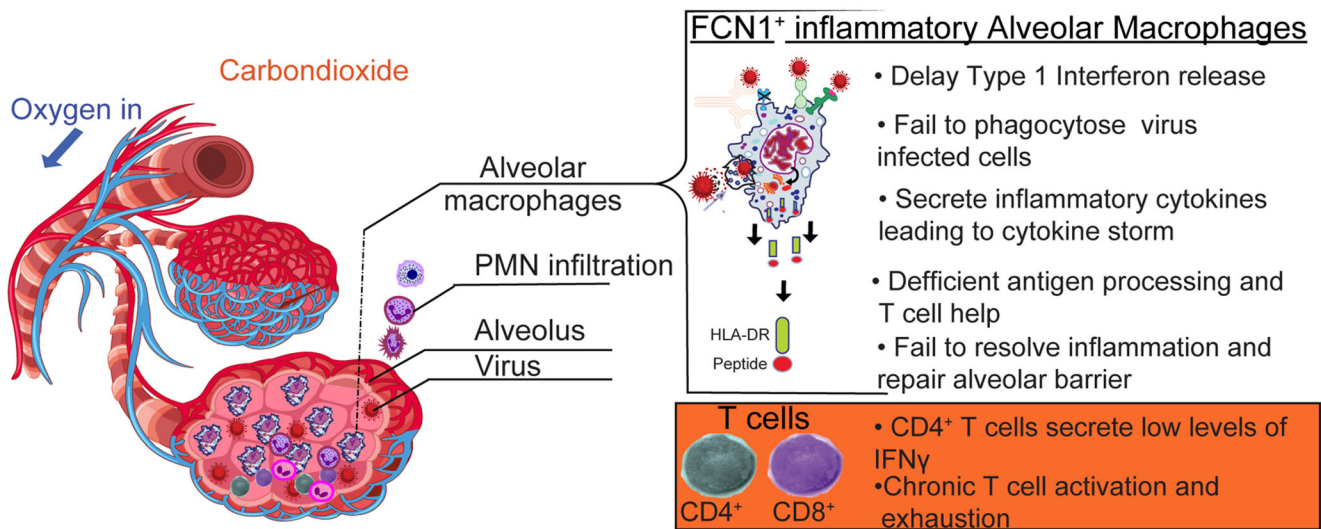inflammation and driving the pathogenesis of SARS-CoV-2 [136]. It has recently been shown that CD169^{+} tissue resident macrophages in the lymph nodes and spleens could serve as viral carriers of SARS-CoV-2 [137]. Similar to what is

Fig 4 Immunological events that lead to severe COVID-19. SARS-CoV-2 evades detection by neutralizing antibodies (nabs). Present non-nabs could contribute to the severity of pathogenesis by causing antibody-dependent enhancement (ADE). Following macrophage detection of the virus, delays in secretion of type 1 interferons avoid antiviral state hence favoring increased viral replication. In addition, macrophage function is dysregulated as evidenced by the failure to resolve inflammation within the lungs, inadequate repairs of the alveolar barrier, damage to the alveolar capillary networks, and increased buildup of debris leads to poor oxygen saturation as demonstrated by bi-lateral ground-glass opacity. In addition, the depletion of alveolar macrophages followed by subsequent enrichment of inflammatory Ficolin-1+ (FCN1^{+}) macrophages, infiltration of polymorphonuclear neutrophils (PMNs) followed by activation of complement pathways lead to exaggerated production of inflammatory cytokines that later sustains a cytokine storm, and fuels systemic pathology.

currently being done to develop long-acting HIV therapy [138–140], repurposing drugs to directly target diverse myeloid carriers such as macrophages may not only lower viral loads but also ensure the timely dissemination of pro-drugs into diverse tissues as these cells could act as drug carriers.

In addition, the intricate role of the stimulation of interferons (IFN) such as IFNα and IFNβ in delaying or exacerbating SARS-CoV-2 is yet to be fully delineated. The five transmembrane PRR referred to as the stimulator of interferon response genes (STING) is expressed in the endoplasmic reticulum of lung alveolar epithelial cells, endothelial cells, and splenocytes. STING senses PAMPs such as damaged DNA, viral nucleic acid sequences, or intermediate products resulting in the stimulation of type 1 IFN responses [141]. Early in infection, SARS-CoV-1 releases viral papain-like-proteases, found within the nsp3 and nsp16 proteins that inhibit STING's downstream IFN secretion [142, 143]. There is no evidence of SARS-CoV-2 dysregulating STING function. However, Berthelot et al. suggest that extensive inflammatory damage associated with severe COVID-19 provides elevated amounts of damaged DNA leading to extensive hyperactivation of STING [141]. This could possibly lead to elevated expression of IFNs that could facilitate the continued infiltration of inflammatory cells such as neutrophils into the lungs and sustain the cytokine storm. Intriguingly, in bats, which are placental mammals that coexist with several coronaviruses and serve as natural reservoirs [144], STING polymorphisims ensure lower IFN secretion that later contributes towards reduced immune pathogenesis [145]. Collectively, these observations highlight the need for further investigation of how STING polymorphisims could affect SARS-CoV-2 immune pathogenesis.

Tracing transmission patterns and evolutionary genomic changes in SARS-CoV-2 while factoring alterations in host immunity could accurately inform epidemiological models that offer reliable predictions on when the number of COVID-19 infections will decrease [146]. Additional studies are required to validate observations that the extent of pathogenicity could vary with different L and S SARS-CoV-2 lineages. Further investigations are also required to cross-validate the differences in pathogenesis observed in the predominant clades of the US west versus east coasts [41].

Recently, Korber et al. provided evidence that the predominant D614 mutation in the SARS-CoV-2 Spike protein is gradually being replaced by G614 mutations in diverse populations worldwide. This newly predominant mutant was shown to have acquired a fitness advantage highlighted by an increased replication capacity that was demonstrated by elevated viral loads. Infection with this variant was also demonstrated by reduced disease severity as measured by extended hospitalization. Lastly, it was also shown that G614 pseudo virions were more prone to neutralization antibodies [147]. Collectively, these results show that within an evolutionary context, SARS-CoV-2 is slowly transitioning into variants that favor suitable host-pathogen interactions [148]. By ensuring enhanced virus replication within a host while limiting host death, the predomianant G614 mutant guarantees better adaptation to the human host in comparisons to the original Wuhan D614 variant. Experiments are currently being conducted to evaluate whether these observed increases in infectivity have any visible effects on transmission dynamics within diverse populations [149]. In addition, an in-depth SARS-CoV-2 report by Kupferschmidt argues that although the G614 mutant easily infects a lab cell line, observations may not be reproducible within the diverse cell types found within a human host [149].

Though datasets such as that of GISAID may not reflect the true dynamism of transmission in resource-limited regions such as Africa, routine evaluation of mutations that occur in these areas is needed to inform the scientific community about how SARS-CoV-2 adapts to regions with endemic tropical co-infections such as HIV, malaria, helminths, and TB [150–152]. There is a need to carry out further research focused on the dynamics of SARS-CoV-2 spread in African Americans as these individuals have been shown to have higher incidences of COVID-19 [153, 154]. Additional studies are warranted to dissect which MHC/HLA-DR polymorphisms across different populations are associated with protection or susceptibility across different populations.

Future studies will also be needed to evaluate whether immunity developed following exposure to SARS-CoV-2 is capable of protection from future encounters with the pathogen [155]. Testing whether repeated exposures boost immunity [156] and evaluating protection from future infection with different SARS-CoV-2 clades without development of deleterious immune responses such as ADE could also inform strategies to design future vaccines. Lastly, extensive research should also be carried out to understand changes that occur in asymptomatic individuals as these persons have been reported to enable the rapid spread of COVID-19 and sustain transmission patterns of the global epidemic [22].

Compliance with ethical standards

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