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

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Review

Genome interaction of the virus and the host genes and non-coding RNAs in SARS-CoV-2 infection

Juliana M. Serpeloni [a], Quirino Alves Lima Neto [b], Léia Carolina Lucio [c], Anelisa Ramão [d], Jaqueline Carvalho de Oliveira [e], Daniela Fiori Gradia [e], Danielle Malheiros [e], Adriano Ferrasa [f], Rafael Marchi [g], David L.A. Figueiredo [h], Wilson A. Silva Jr. [i], Enilze M.S.F. Ribeiro [e], Ilce M. S. Cólus [a], Luciane R. Cavalli [g,*]

[a] Departamento de Biologia Geral, CCB, Universidade Estadual de Londrina, Londrina, PR, Brazil
[b] Departamento de Ciências Básicas da Saúde, CCS, Universidade Estadual de Maringá, Maringá, PR, Brazil
[c] Programa de Pós-graduação em Ciências Aplicadas à Saúde, CCS, Universidade Estadual do Oeste do Paraná, Francisco Beltrão, PR, Brazil
[d] Departamento de Ciências Biológicas, Universidade Estadual do Centro-Oeste, Guarapuava, PR, Brazil
[e] Departamento de Genética, SCB, Universidade Federal do Paraná, PR, Brazil
[f] Departamento de Informática, SECATE, Universidade Estadual de Ponta Grossa, Ponta Grossa, PR, Brazil
[g] Instituto de Pesquisa Pelé Pequeno Príncipe, Faculdades Pequeno Príncipe, Curitiba, PR, Brazil
[h] Departamento de Medicina, Universidade Estadual do Centro-Oeste, UNICENTRO e Instituto de Pesquisa para o Câncer, IPEC, Guarapuava, PR, Brazil
[i] Departamento de Genética, Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, SP, e Instituto de Pesquisa para o Câncer, IPEC, Guarapuava, PR, Brazil

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ABSTRACT

In this review, we highlight the interaction of SARS-CoV-2 virus and host genomes, reporting the current studies on the sequence analysis of SARS-CoV-2 isolates and host genomes from diverse world populations. The main genetic variants that are present in both the virus and host genomes were particularly focused on the *ACE2* and *TMPRSS2* genes, and their impact on the patients' susceptibility to the virus infection and severity of the disease. Finally, the interaction of the virus and host non-coding RNAs is described in relation to their regulatory roles in target genes and/or signaling pathways critically associated with SARS-CoV-2 infection. Altogether, these studies provide a significant contribution to the knowledge of SARS-CoV-2 mechanisms of infection and COVID-19 pathogenesis. The described genetic variants and molecular factors involved in host/virus genome interactions have significantly contributed to defining patient risk groups, beyond those based on patients' age and comorbidities, and they are promising candidates to be potentially targeted in treatment strategies for COVID-19 and other viral infectious diseases.

1. Introduction

The Coronavirus disease 2019 (COVID-19), a worldwide pandemic disease with high mortality rates, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The genome sequence of this virus classifies it as a new virus in the *Coronaviridae* family, and other members of the same family, such as SARS-CoV-1 and MERS-CoV, have been identified to infect humans.

Considerable variation in the clinical symptoms and progression of COVID-19 disease are observed among patients infected with SARS-CoV-2, which cannot be completely explained by age and/or the presence of comorbidities (Guan et al., 2020). In addition, infectivity and lethality are not linearly related. This clinical variability suggests that host genetics (i.e., genomic variants) play a strong role in the susceptibility and impact of the manifestation of COVID-19 (COVID-19 Host Genetics Initiative, 2020; Ovsyannikova et al., 2020).

In this review, we present research studies on the genome interaction of SARS-CoV-2 and host cells, performed both in virus isolates from different countries and in host genomes from diverse human populations. In particular, these studies focused on the identification and

* Corresponding author at: Instituto de Pesquisa Pelé Pequeno Príncipe, Faculdades Pequeno Príncipe Avenida Silva Jardim, 1632, Água Verde, Curitiba, PR 80250-060, Brazil.
E-mail address: luciane.cavalli@pelepequenoprincipe.org.br (L.R. Cavalli).

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Table 1
Gene variants in the SARS-CoV-2 virus genome.

Genome coverage	Methodological approach	Main results	Reference
Whole genome	– Genome sequencing and alignment analysis of 7710 GISAID[a] sequences	– Average pairwise difference of 9.6 SNPs between any two genomes – Mutation rate of the global diversity of SARS-Cov2 of ~6 × 10-4 nucleotides/genome/year – 290 aminoacid alterations in the genomes: 232 synonymous and 58 non-synonymous mutations	Khailany et al., 2020
Whole genome	Analysis of SARS-CoV-2 sequences using CoV_GLUE (http://cov-glue.cvr.gla.ac.uk) of 9028 available sequences, including 4973 European sequences	– Divergence of the two main mutations (S-D614G and nsp12-P323L) from the NCBI (NC_045512) retrieved in all continents with only three cases in Asia – Mutations at ORF8-L84S and ORF3a-Q57H (as the third and fourth most frequent mutation, respectively) – Co-evolving of the L84S amino acid substitution with three other mutations: nsp4-F308Y, ORF3a-G196V and N-S197L	Coppée et al., 2020
Whole genome	Genome sequencing and alignment analysis of 94 Genbank genomes	– 156 variants and 116 unique variants across the genome (46 missense, 52 synonymous, 2 insertion, 1 deletion and 14 non-coding alleles) – C > T and or T > C as the most common variants in the ORF1ab (NSP1-NSP16), ORF8 and, N genes	van Dorp et al., 2020
Whole genome	Genome sequencing and alignment analysis of ~660 genomes- NCBI[b] virus database	– Mutations in the S protein (D614G, V483A, L5F, Q675H, H655Y, and S939F) – Substitutions at R203K and G204R in the N protein – Substitutions at L84S, V62L, and S24L in the ORF8 – Non-synonymous mutations in ORF3a (Q57H and G251V – Non-synonymous mutations in ORF1ab (T265I, P4715L, P5828L, and Y5865C)	Laha et al., 2020
Whole genome	RNA sequencing analysis of NCBI RNA-seq data	– A-to-G (59.1%) RNA modifications (caused by RNA deamination) – Non-A-to-G variations, G to A (22,4%) and others (18,5%) (caused by replication errors) – A-to-G alterations in the N (>de 40%), ORF1AB (~35%), S, M, E, ORF3A, ORF8, ORF7A, and ORFA6 genes	Li et al., 2020b
Whole genome	Genome sequencing and alignment analysis of 12,909 genomes/estimation of common ancestor (TMRCA[c]) and mutation rates	– Indication that COVID-19 might have originated earlier than and outside of Wuhan Seafood Market – The genetic polymorphism patterns, including the enrichment of specific haplotypes and the temporal allele frequency trajectories generated from infection clusters, are similar to those caused by evolutionary forces such as natural selection	Liu et al., 2020a
Whole genome	Genome sequencing and alignment analysis of 106 NCBI genomes	– Higher number of mutations in the S protein, Nsp1, RdRp and the ORF8 regions – 47 key point mutations/SNPs located along the entire genome sequence in isolates from 12 different countries – NSP1 and ORF8 as the two hot spots with mutations and deletions	Vankadari, 2020
Whole genome	Genome sequencing and alignment analysis of 167 sequences from 15 distinct geographical locations	– 290 sites with variations (S, M and N genes; orf1ab, orf3a, in the envelope protein-coding gene, orf6, orf8, orf7b and orf10) – 244/290 variants were of a nucleotide substitution (158 transitions and 86 transversions) – High similarity (>99.9%) amongst all locations	Parlikar et al., 2020
Whole genome	Genome sequencing and alignment analysis of 566 genomes from India compared to NCBI	– 933 substitutions, 2449 deletions and 2 insertions, in total 3384 unique point mutations: distributed in 100 clusters of mutations (mostly deletions); 1609 substitution, deletion and insertion point mutations, 64 SNPs in coding regions and 7 in 5′-UTR and 3′-UTR – Largest number of SNPs in coding regions of ORF1ab and Spike protein	Saha et al., 2020
Whole genome	Genome sequencing and alignment analysis of 86 GISAID genomes from 12 countries	– 3 deletions (2 ORF1ab polyprotein and one in the 3′ end of the genome) in the genomes from Japan, USA, and Australia – 42 missense mutations (non-structural and structural proteins): 29 in the ORF1ab polyprotein, 8 in the S glycoprotein, 1 in the matrix protein, and 4 in the nucleocapsid protein	Phan, 2020
Whole genome	Genome sequencing and alignment analysis of 30,366 genomes/software developed by the researcher's group (ODOTool[d])	– 11 variations, with the incidence of over 10% in the 30,366 isolates – 8 of these variations (C1059T, G11083T, C14408T, A23403G, G25563T, G28881A, G28882A, and G28883C) caused amino acid substitutions	Ugurel et al., 2020
Whole genome, D614G mutation (gene spike protein)	Statistical analysis of the D614G mutation of 2795 GISAID genomes from 55 countries	– Amino acid change from an aspartate to a glycine residue at position 614 (D614G)	Isabel et al., 2020

(*continued on next page*)

Table 1 (*continued*)

Genome coverage	Methodological approach	Main results	Reference
Whole genome, *ACE2* binding domain	Mutation analysis of 34 human and animal isolates	– High frequency of the D614G mutation (87%) among Italians isolates – D614G clade report of 954 of 1449 (66%) European isolates and 1237 of 2795 (44%) worldwide isolates – 60% of nucleotide variations between human SARS-CoV-2 and bat RaTG13, can be attributed to C > U and U > C substitutions – An accumulation of C > U mutations was observed in SARS-CoV2 variants in the human population, suggesting a significant role in the evolution of the SARS-CoV-2 coronavirus	Matyášek and Kovařík, 2020
Whole genome, Spike protein	Genome sequencing and alignment analysis of 1,325 genomes and 1604 CDS[e] of spike proteins from NCBI database	– 1197 SNPs, classified in 782 clusters – 1604 CDS at the S protein – Two major phylogenyclades A and B with many subclades in the S protein of SARS-CoV-2 circulating worldwide – 23402A > G SNP in 48.2% (the most common)	Singh et al., 2020
Spike gene	Development of a bioinformatics pipeline for Spike amino acid variants-GISAID data	– A spike protein amino acid change at D614G – Association of the D614G variant with high levels of infectivity and viral loads	Korber et al., 2020
ORF8	Evolutionary analysis of ORF8: genetic diversity and genomic rearrangements	– The ORF8 is poorly conserved among coronaviruses with a small number of highly frequent lineages – Nonsense mutations and three main deletions in the ORF8 gene that either remove or significantly change the ORF8 protein, which suggests that SARS-CoV-2 can persist without a functional ORF8 protein	Pereira, 2020
Orf1a, Orf1b, ORF3a ORF6, ORF7a, ORF8, ORF10, S, E, M, N, Sum	Metatranscriptome sequencinganalysis of eight fluid bronchoalveolar lavage from 25 community-acquired pneumonia patients and 20 healthy controls (Wuhan, China)	– No specific polymorphism was described – The median number of intra-host variants (iSNVs) was 1–4 in SARS-CoV-2 infected patients – SARS-CoV-2 evolves *in vivo* after infection, which may affect its virulence, infectivity, and transmissibility	Shen et al., 2020
RdRp, S, and Nsp-2	Sanger sequencing of the NSP-2, NSP-12, and S genes for phylogenetic analysis of 7 cases from Iran	– NSP-2 sequences - highest similarity between Iranian and Wuhan (China) – RdRp and S gene sequences-highest similarity between Iranian and China and USA – No identified differences between Iranian isolates	Tabibzadeh et al., 2020
S, RdRP, RNA primase, nucleoprotein	Genotyping of 558 isolates worldwide	– Mutations in genes encoding the S proteins and RNA polymerase, RNA primase, and nucleoprotein – Classification of the SNPs into four major groups: single mutation in nsp6 (11083G > T) (115%), single mutation in ORF3a (26144G > T) (49%), single mutation in RNA polymerase (nsp8) (8782C > T, 28144 T > C) (140%), and double mutations in S protein and RNA polymerase: (241C > T, 3037C > T, 14408C > T, 23403A > G) (178%; 182%; 182%; 183%) – Predominance of co-mutations (241C > T, 3037C > T, 23403A > G) in isolates from Europe – Estimated transmission of SARS-CoV-2 of 14 generations since its first infection to humans in Dec 2019	Yin, 2020

[a] GISAID: Global Initiative on Sharing All Influenza Data.
[b] NCBI: National Center for Biotechnology Information.
[c] TMRCA: Time to the most recent common ancestor.
[d] ODOTool: Strategy Based Local Alignment Tool.
[e] CDS: Coding Sequence.

understanding of the role of critical SNPs and other genetic variants in both virus and host genomes as well as of non-coding RNAs (miRNAs and lncRNAs) and their target gene regulation and potential therapeutic application.

2. SARS-CoV-2 genome variants

RNA (ssRNA) viruses, such as the SARS-CoV-2, present a high mutation rate (Duffy, 2018), resulting in the diversity of their genome and the appearance of variants that can facilitate their adaptive capacity to different environments. However, contrary to other RNA viruses, coronaviruses present a repair proofreading function, performed by the NSP14 exoribonuclease, which is highly conserved and very likely essential for the maintenance of the viral genome replication (Robson et al., 2020).

Extensive sequencing-based analysis has been performed in SARS-CoV-2 isolates, in order to determine the genome of the distinct virus isolates and to compare them with other RNA viruses (Coppée et al., 2020; Isabel et al., 2020; Khailany et al., 2020; Korber et al., 2020; Laha et al., 2020; Li et al., 2020b; Liu et al., 2020a; Matyášek and Kovařík, 2020; Phan, 2020; Parlikar et al., 2020; Pereira, 2020; Saha et al., 2020; Shen et al., 2020; Singh et al., 2020; Tabibzadeh et al., 2020; Ugurel et al., 2020; van Dorp et al., 2020; Vankadari, 2020; Yin, 2020; Bianchi et al., 2021) (Table 1). In general, these studies have demonstrated a high similarity between the genome sequences of SARS-CoV-2 and SARS-CoV-1. Data from the Global Initiative on Sharing All Influenza Data (GISAID) indicated that the SARS-CoV-2 mutational rate is similar to that of other CoVs (https://www.gisaid.org/hcov19-variants/).

The most frequent variations that have been reported in the SARS-CoV-2 genome are single nucleotide polymorphisms (SNPs) and single nucleotide variants (SNVs). These variations, which are found in both the non-coding or coding regions of the viral genome, are the main cause of the genetic diversity and evolution of the virus as well as of its virulence and transmissibility (Khailany et al., 2020). The coding regions

affect genes that encode the following viral proteins: spike (S), RNA polymerase, RNA primase, nucleoproteins and open reading frames (ORFs). Among the ORFs genes, are included the: ORF1a, ORF1b, ORF3a, ORF6, ORF7a, ORF8 and ORF10. SNPs located in the coding regions of the spike and RNA polymerase proteins have been associated with the efficiency of the vaccines (COVID-19 Host Genetics Initiative, 2020). Intrahost single nucleotide variants (iSNVs) have also been reported in sequences of SARS-CoV-2, showing the variation in the virus genome after the infection (Shen et al., 2020).

In addition to these variants, point mutations, such as substitutions, insertions, and deletions, are also found in the SARS-CoV-2 genome. Saha et al., (2020) described 3384 point mutations in genomic sequences of the CoV-2 from Indian patients, including 2449 deletions and 933 nucleotide substitutions. In an Iranian study, a comparison of the short segments of genes that encode the nonstructural Protein 2 (NSP-2), RNA-dependent RNA polymerase (RdRp), and the spike protein, showed however, no significant difference within the sequences of the studied population. Nonetheless, a phylogenetic analysis of the Iranian variant has shown that the SARS-CoV-2 virus strains are similar to those from China and the USA (Tabibzadeh et al., 2020).

In late 2020, new variants of concern (VOCs) were identified, being potentially associated with higher levels of transmissibility and severity of COVID-19 (Cascella et al., 2021). The main variants include the alfa, beta, gamma and delta variants (World Health Organization (WHO); SARS-CoV-2 Variants of Concern and Variants of Interest; Geneva, WHO; 2021; https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/) that affect the spike protein, which mediates the entry of the virus into host cells (Shang et al., 2020). The B.1.1.7 lineage (VOC 202012/01 or 20I/501Y. V1), called the alpha variant, was the first described variant in the United Kingdom (UK) (Davies et al., 2021a). This variant virus genome presents 17 mutations with eight in the spike protein (Δ69-70 deletion, Δ144 deletion, N501Y, A570D, P681H, T716I, S982A and D1118H) (Walensky et al., 2021), and it has been associated with an increased severity of disease compared to other circulating virus variants (Davies et al., 2021b; Volz et al., 2021). The B.1.351 lineage (501Y. V2), called the beta variant, was described in South Africa (Tegally et al., 2021), and its genome presents nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G and A701 V) in the spike protein (Wibmer et al., 2021). In January 2021, the third variant of concern, the B.1.1.248 lineage (501Y. V3 or P.1 lineage), called the gamma variant, was reported in Brazil in the state of Manaus (Faria et al., 2021), presenting 15 mutations with 10 in the spike protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K and N501Y). The latter three mutations (K417T, E484K and N501Y) are associated with increased binding to the human angiotensin-converting enzyme 2 (ACE2) receptor. As the beta variant, B.1.1.248 presents higher transmission rates and reduced neutralization by monoclonal antibody therapies, convalescent sera and post-vaccination sera (Tada et al., 2021). Finally, the B.1.617 lineage, called the delta variant, was first detected in India, presenting nine mutations in the spike protein (T19R, G142D, Δ156, Δ157, R158G, L452R, T478K, P681R and D950N) (Planas et al., 2021). This variant has been shown to have high transmissibility with cases rapidly spreading to other countries and a reduced antibody neutralization effect (Campbell et al., 2021; Liu and Ginn, 2021; Planas et al., 2021).

Altogether, these studies have shown that SARS-CoV-2 genome variants directly impact the infection rates, immune escape and the clinical characteristics of COVID-19. Therefore, these variants can be used as epidemiological tools for the tracking and monitoring of the virus and to control the infection outbreaks worldwide. A description of these studies, with their respective main results, is presented in Table 1.

3. Host genome variants and SARS-CoV-2 susceptibility

In the COVID-19 pandemic, several underlying medical conditions, comorbidities and aging in addition to interactions between genetic and environmental/epigenetic factors, such as smoking, alcohol and obesity, have been reported as risk factors for SARS-CoV-2 infection, influencing the severity of the disease and susceptibility to the disease (Yamamoto et al. 2021). In addition to the large clinical variability observed in patients infected with SARS-CoV-2, the host genetic background also plays a strong role in the progression of COVID-19. After attaching itself to host cells with its spike protein, SARS-CoV-2 uses the ACE2 receptor and the TMPRSS2 enzyme to enter the cells to use the host machinery to replicate its RNA (Hoffmann et al., 2020). Therefore, *ACE2, TMPRSS2* and their variants have been considered the main molecular markers that confer genetic susceptibility or resistance to COVID-19.

The ACE2 receptor is a type I transmembrane glycoprotein consisting of 805 amino acids. The *ACE2* gene presents 265 missense SNPs, including in-frame insertions and deletions. Among these, 194 SNPs were found with allelic frequencies by considering the 1000 Genomes Project Data, the Exome Aggregation Consortium Data, and the Genome Aggregation Data (Darbani, 2020). *ACE2* expression differs based on the biological age and sex of the individual (Ovsyannikova et al., 2020). The *ACE2* gene is located on the X-chromosome (Xp22.2) and, apparently, men present higher levels of *ACE2* expression in lung tissue than women (Lippi et al., 2020).

Polymorphisms of the *ACE2* gene have also been shown to vary according to the different ancestry and geographic distribution of COVID-19 patients. For example, the Asian population expresses ACE2 at higher levels than European and African-American populations (Lippi et al., 2020). Using *in silico* tools, Calcagnile et al. (2021) reported the following two distinct SNPs that may potentially affect the interaction of *ACE2* with the SARS-CoV-2 spike protein: 1) S19P, which is common in African populations and decreases the virus-receptor affinity; and 2) K26R, which is common in European populations and increases the virus-receptor affinity. In European patients, another study has reported the association of the rs2285666 *ACE2* variant with hypertension in an elderly population without conferring significant clinical differences of COVID-19 (Gómez et al., 2020). Finally, in East Asian populations, a distinct distribution of 11 common variants and one rare variant associated with enhanced ACE2 receptor expression has been shown to influence the levels of susceptibility to SARS-CoV-2 infection (Cao et al., 2020). These and additional *ACE2* genotyping studies (Benetti et al., 2020; Calcagnile et al., 2021; Cao et al., 2020; Darbani, 2020; Gómez et al., 2020; Hussain et al., 2020; Li et al., 2020a; Lippi et al., 2020; Pati et al., 2020; Torre-Fuentes et al., 2020; Yamamoto et al., 2020) are presented in Table 2.

Another gene homologous to *ACE2*, the human *ACE1* gene on chromosome 17q23.3, has also been associated with SARS-CoV-2. The *ACE1* gene has known polymorphisms in intron 16, including an insertion (I) or deletion (D) of a 287-base pair (bp) Alu repeat sequence (Yamamoto et al., 2020). The *ACE1 II* genotype frequency has been observed to be negatively correlated with the number of SARS-CoV-2-infected cases and deaths (Yamamoto et al., 2020). In contrast, the D/I polymorphism has been observed to be associated with reduced expression of *ACE2* levels, rendering patients less susceptible to infection by decreasing receptor-spike protein interactions (Delanghe et al., 2020). Interestingly, Hatami et al (2020) reported that an increase in the D/I allele frequency ratio increases the recovery rate of COVID-19 patients. Finally, in Spanish individuals, the *ACE1*-D/I polymorphism is associated with the risk of developing severe forms of COVID-19, which is related to the hypertension status of the patients (Cao et al., 2020). In these individuals, no association of the DD genotype with the risk of developing COVID-19 has been observed. However, asymptomatic individuals have not been evaluated; therefore, the conferred resistance of this genotype to viral infection cannot be excluded (Cao et al., 2020). However, recent studies have reported an association of DD polymorphisms in patients with severe disease (Verma et al., 2021), including thromboembolism (Calabrese et al., 2021).

The *TMPRSS2* gene, which is involved in the proteolytic cleavage of ACE2 and the SARS-CoV-2 spike protein, leads to viral penetration into

the host cell and is essential for viral spread and pathogenesis in the infected host (Torre-Fuentes et al., 2020). *TMPRSS2,* located at 21q22.3, is an androgen-responsive gene, which may explain pronounced COVID-19 severity in males according to Asselta et al. (2020). The eQTL variant of *TMPRSS2* nonsynonymous SNPs (rs12329760 encoding p. Val160-Met) is associated with genetic susceptibility to COVID-19 as well with risk factors, such as cancer and male sex (Hou et al., 2020).

The rs35074065 eQTL variant is associated with high expression of *TMPRSS2* but with a low expression of the interferon (IFN)-α/β-inducible gene, *MX1* (Russo et al., 2020). Senapati et al. (2020) showed that four *TMPRSS2* variants (rs112657409, rs11910678, rs77675406 and rs713400) influenced its expression. Torre-Fuentes et al. (2020) found an association between two synonymous variants (rs61735792 and rs61735794) and the rs75603675 with SARS-CoV-2 infection.

Polymorphisms in other genes unrelated to *ACE1/2* and *TMPRSS2* have been associated with susceptibility to SARS-CoV-2 infection, including polymorphisms in the *HLA* (Lorente et al., 2020; Nguyen et al., 2020; Tomita et al., 2020) and ABO blood group (Ellinghaus et al., 2020; Zhao et al., 2020) genes as well as in other genes (Qian et al., 2021; Hubacek et al., 2021; Maiti, 2020; Schönfelder et al., 2021), such as the *IF1H1* gene (rs1990760; (C > T)), a cytoplasmic viral RNA receptor that activates interferon signaling (Qian et al., 2021) **(**Table 2**).** In a genome-wide association study (GWAS), Ellinghaus et al. (2020) found that the following two *loci* associated with COVID-19 induce respiratory failure: the rs11385942 insertion–deletion at *locus* 3p21.31 (containing six genes: *SLC6A20, LZTFL1, FYCO1, CXCR6, XCR1,* and *CCR9*) and the rs657152 A or C SNP at *locus* 9q34.2 (which determines the ABO blood groups). Interestingly, genetic variants that are most associated with severe forms of COVID-19 on chromosome 3 (chr3: 45, 859, 651–45, 909, 024 and *hg19*) are in high linkage disequilibrium, i.e., they are all strongly associated in the population and are transmitted as a haplotype. This haplotype, a genomic segment of nearly 50 kb, was inherited from the Neanderthals. Among the individuals in the 1000 Genomes Project, the "Neanderthal core haplotype" is almost completely absent in Africa but occurs in South Asia at a frequency of 30%, in Europe at 8%, among admixed Americans at 4% and at lower frequencies in East Asia. Therefore, it has been suggested that the "Neanderthal haplotype" may be a substantial contributor to COVID-19 risk in certain populations (Zeberg and Pääbo, 2020).

In relation to the blood type, individuals in blood groups A and O present a significantly higher and lower risk for acquiring COVID-19, respectively. According to Arend (2021), it is possible that the essential link between the host and SARS-CoV-2 at the initial phase of infection as well as the nonviral pathogenesis may not be represented by a hybrid peptide but instead by an intermediate hybrid O-glycan, a serologically classical A-like/Tn O-glycan structure, considering the following characteristics: (i) the most critical molecular step in the pathogenesis of SARS-CoV-2 is the mobilization of the viral serine molecule; (ii) serine residues are the target glycosides of phenotype-determining saccharides of A and B blood groups; (iii) severe symptoms of COVID-19 occur preferentially in individuals with non-O blood groups; (iv) the susceptibility of individuals with A blood group to infections with *Plasmodium falciparum*, the pathogen of malaria tropical, is similar to infections with SARS-CoV-2; and (v) the ABO(H) phenotype development is molecularly connected to the development of humoral innate immunity.

The above studies (summarized in Table 2) have increased the knowledge of the genetic variations associated with SARS-CoV-2 transmission and pathogenesis at both the individual and population levels, and they have enabled the identification of individuals at high risk of infection and the subsequent development of the disease with distinct severity. Considering that there is still no specific therapy for COVID-19 and that emerged genetic variants affect many infected people, continuing epidemiological and molecular biological studies are required to understand the pathogenesis of this disease and its mechanisms of infection and dissemination.

4. MiRNAs and SARS-CoV-2 infection

MicroRNAs (miRNAs), non-coding small RNA molecules, are important posttranscriptional regulators in various organisms, ranging from viruses to higher eukaryotes (Bartel, 2004). Dysregulated miRNA expression is associated with the development of pathological processes and chronic diseases, including those caused by viral infections (Girardi et al., 2018).

Beyond the well-characterized endogenous genome expression modulation, human host miRNAs can interact with several RNA viruses, including the SARS-CoV-2. Similarly, the virus-encoded miRNAs can also bind to human miRNAs (Girardi et al., 2018; Mishra et al., 2020; Marchi et al., 2021). In fact, one of the conditions for the success of the pathogenic SARS coronaviruses depends on their ability to suppress intracellular antiviral pathways in host cells (Girardi et al., 2018).

MiRNAs of viral origin present a double function, regulating the expression of both viral mRNAs and cellular (host) miRNAs (Girardi et al., 2018; Mishra et al., 2020). Although this function has not yet been completely elucidated, it is suggested that viral miRNAs likely act on cellular genes involved in processes that facilitate viral replication, induce latency, prevent apoptosis and/or cause immune evasion. Additionally, the virus genome may also function as a sponge of host miRNAs, interfering in gene regulation via a mechanism known as competing endogenous RNAs (ceRNAs) (Bartoszewski et al., 2020). In the host, however, the intracellular presence of the virus triggers the deregulated expression of several endogenous miRNAs to induce an immune response and mediate an antiviral reaction. This host-response-gene network occurs through the miRNA transcriptional regulation of a subset of mRNA gene targets, which are critical components of signaling pathways that affect virus pathogenicity and cellular response, including the WNT, INF, PIK3/AKT, MAPK and NOTCH pathways (Girardi et al., 2018; Mishra et al., 2020).

In COVID-19, few studies on miRNA analysis have been conducted in biological samples of the patients (Centa et al., 2020; Bagheri-Hosseinabadi et al., 2021; Li et al., 2021). The identification of the potential virus-human miRNA-based interactions has mainly been based on computational miRNA prediction analysis (for review: (Marchi et al., 2021). The general prediction mechanism of putative miRNAs is based on seed region specificity. The seed sequence, which is the critical part of target prediction, is essential for the binding of miRNAs to target mRNAs (Bartel, 2004). In a prediction-based study, Arisan et al. (2020) selected SARS-CoV-2 genome sequences from different geographical regions (China, Italy, Spain, the UK and Turkey) in the PubMed and GISAID databases, and they compared the sequences to those from SARS, MERS and two common cold coronaviruses (OC43 and 229E) using the miRBase database to identify the presence of miR-like sequences. The authors identified seven distinct miRNAs (miRs 8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p and 1468-5p) among these viruses, highlighting considerable differences between the sequences of other viruses and the sequences of SARS-CoV-2. The seven miRNAs identified are significantly associated with KEGG pathways linked to virus pathogenicity and host responses (Arisan et al., 2020).

Fulzele et al. (2020) identified 558 common human cellular miRNAs targeting both SARS (4 isolates) and SARS-CoV-2 (29 isolates from different regions) genomes as well as 315 miRNAs uniquely targeting the SARS-CoV-2 genome. Interestingly, both KEGG and GO pathway analyses revealed that some of these miRNAs are involved in several age-related complications and suggested that they might be a contributing factor for the increased severity and mortality in individuals with advanced age and with comorbidities. Chow and Salmena (2020) identified 128 human miRNAs potentially targeting the SARS-CoV-2 genome with 28 and 23 of them targeting the SARS-CoV and MERS-CoV genomes, respectively, and they reported that 5 of the identified miRNAs (miR-16-2-3p, miR-139-5p, miR-155-3p, miR-1275 and let7a-

Table 2
Gene variants in the host genome in association with genetic susceptibility and clinical characteristics in SARS-CoV-2 infected patients.

Gene	Methodological approach	Main results	Reference
ACE2[a], *CTSB*[b], *CTSL*[c], *TMPRSS2*[d]	*In silico* analysis of SNP data from 1000 Genomes Project, Exome aggregation consortium, and Genome aggregation	– Identification of several specific and common *ACE2* variants with relevance to the viral entry and infection – Association of the hemizygous viral-entry booster variants of *ACE2* with higher SARS-CoV-2 mortality rate in males	Darbani, 2020
ACE2	Review article on *ACE2* polymorphisms	– *ACE2* polymorphisms may modulate intermolecular interactions with the SARS-CoV-2 spike protein and/or worsen pulmonary and systemic injury in patients with COVID-19 – *ACE2* X-chromosome linked phenotype could be related to higher risk of COVID-19 in the male sex	Lippi et al., 2020
ACE2	In silico analysis of the impact of *ACE2* SNPs on the interaction with SARS-CoV-2 spike glycoprotein	– Decrease and increase of *ACE2* affinity for SARS-CoV-2 spike protein by the S19P (rs73635825, common in Africans) and K26R (rs75548401, common in Europeans) substitutions, respectively. – S19P may protect and K26R may predispose to severe SARS-CoV-2 disease	Calcagnile et al., 2020
ACE1[e], *ACE2*	Analysis of the *ACE1* I/D and *ACE2* rs2285666 polymorphisms of 204 COVID-19 patients (137 non-severe and 67 severe-ICU) and 536 age-matched controls	– Association of *ACE1*-I/D polymorphism with the risk of severe COVID-19 depending on the hypertension status – Association of *ACE2* rs2285666 variant with hypertension in elderly population, without difference between mild and severe forms of COVID-19	Gómez et al., 2020
ACE2	Analysis of the 1700 variants in *ACE2* gene region from ChinaMAP[m] and 1KGP[n]	– No direct evidence of SARS-CoV-2 spike protein binding-resistant *ACE2* mutants in different populations – Association of higher allelic frequency in the eQTL variants with higher *ACE2* expression in the East Asian populations	Cao et al., 2020
ACE2	Whole-exome sequencing (WES) data mining for *ACE2* variants of 6930 Italian individuals from five different centers	– Missense changes (Asn720Asp, Lys26Arg, and Gly211Arg) predicted to interfere with ACE2 structure and stabilization – Interference of rare variants (Leu351Val and Pro389His) with SARS-CoV-2 spike protein binding – Higher allelic variability of *ACE2* in the comparison of *ACE2* WES data between 131 patients and 258 controls	Benetti et al., 2020
ACE2	Construction of intermolecular interactions of molecular models of native and variants of *ACE2* and ACE2-spike protein complex	– Variations in the intermolecular interactions of the *ACE2* alleles, rs73635825 (S19P) and rs143936283 (E329G) with the viral spike protein	Hussain et al., 2020
ACE2	Molecular dynamic simulation on the influences of *ACE2* mutant on protein structure. Calculations of the binding free energies between S protein and ACE2. Analysis of *ACE2* gene expression in eight global populations from HapMap3[o]	– Significant differences of minor *ACE2* AF of four missense mutations between Asians and Caucasians – K26R and I468V variants may affect binding between S protein and ACE2 receptor – Marginal differences in gene expression for some populations in HapMap3 as compared to the Chinese population	Li et al., 2020a
ACE2	Epidemiological investigation of the association between *ACE2* I/D polymorphism with SARS-CoV-2 infection, mortality rate, and percentage of recovery in Asians	– Positive correlation of D allele of *ACE2* polymorphism with SARS-CoV-2 infection and mortality rate in Asians – *ACE2* I/D polymorphism has no role in the recovery rate of the patients	Pati et al., 2020
ACE1, ACE2, CTSL, TMPRSS2	Genotype analysis from high-coverage sequenced data of 1KGP (phase 3) and the Korean Personal Genome Project	– Negative correlation of *ACE1* II with the number of SARS-CoV-2 cases and deaths – No correlation of *ACE2*, *CTSL* and *TMPRSS2* with COVID-19 prevalence or mortality	Yamamoto et al., 2020
ACE1	Collection of the literature data on the geographical variation of the *ACE1* I/D polymorphism	– Correlation of *ACE1* polymorphisms with the prevalence of COVID-19 – Association of the I/D polymorphism in intron 16 of *ACE1* with reduced expression of *ACE2*	Delanghe et al., 2020
ACE1	Meta-analysis on the prevalence of *ACE* (I/D) genotype in countries most affected by the COVID-19	– Association of the increase of the I/D allele frequency ratio with the patients' recovery rate – No significant differences in the death rate	Hatami et al., 2020
ACE1	*ACE* I/D polymorphism involvement in COVID-19 patients with pulmonary embolism	– Presence of *ACE1* D/D polymorphisms higher in patients with thromboembolism in COVID 19 disease	Calabrese et al., 2021
ACE1	Association of *ACE1* I/D polymorphism with severity of COVID-19 in 269 cases	– Association of *ACE1* DD genotype, frequency of D allele, older age (≥46 years), unmarried status, and presence of diabetes and hypertension in severe COVID-19 patient	Verma et al., 2021
ACE2,TMPRSS2	Analysis of whole-exome sequencing and SARS-CoV-2 infection in a familial multiple sclerosis cohort	– Low level of *ACE2* polymorphisms, with only 2 variants (rs41303171 and rs35803318) – High level of *TMPRSS2* polymorphisms – Association of the *TMPRSS2* rs61735794 and rs61735792 with SARS-CoV-2 infection	Torre-Fuentes et al., 2020
ACE2, TMPRSS2		– No association between *ACE2* and COVID19 severity/sex bias in the Italians	Asselta et al., 2020

(*continued on next page*)

Table 2 (*continued*)

Gene	Methodological approach	Main results	Reference
	Comparison of the rare-variants burden and polymorphisms frequency from exome and SNP-array data of a large Italian cohort from Europe and East Asia	– Differences of exonic variant (Val160Met) between East Asians and Italians – Higher frequency of rare alleles of 2 haplotypes, predicted to induce higher levels of *TMPRSS2* in the Italian compared to the East Asian population	
ACE2, TMPRSS2	Analysis of *ACE2* and *TMPRSS2* polymorphisms of 81,000 human genomes	– Association of *ACE2*- Arg514Gly polymorphism with cardiovascular and pulmonary conditions in the African/African American populations – Suggestive association of the *TMPRSS2 eQTL*: Val160Met (rs12329760) with genetic susceptibility to COVID-19	Hou et al., 2020
TMPRSS2	Analysis of coding-region variants in *TMPRSS2* and the eQTL[p] variants	– Association of the eQTL variant rs35074065 with high expression of *TMPRSS2* and low expression of the *IFN*-α/β-inducible gene	Russo et al., 2020
TMPRSS2, CD26[f]	Analysis of the coding (missense) and regulatory variants of the *TMPRSS2* and *CD26* genes from 26 global populations	– Four regulatory variants in the *TMPRSS2* gene (rs112657409, rs11910678, rs77675406 and rs713400) influenced its expression – Significant role of the *CD26*: rs13015258 in genes involved in SARS-CoV-2 internalization	Senapati et al., 2020
HLA[g]	Genotyping analysis of *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1* and *HLA-DQB1 loci* in 72 COVID-19 patients and 3,886 controls	– *HLA-A**11, *HLA-C**01 and *HLA-DQB1**04 alleles associated with higher mortality	Lorente et al., 2020
HLA	*In silico* analysis of viral peptide-MHC[q] class I binding affinity across all known *HLA-A*, *-B*, and *-C* genotypes for all SARS-CoV-2 peptides	– *HLA-B**46:01 presented the fewest predicted binding peptides – *HLA-B**15:03 showed the greatest capacity to present highly conserved SARS-CoV-2 peptides	Nguyen et al., 2020
HLA	*In silico* analysis of the association of *HLA* gene polymorphisms with prevalence and mortality of COVID-19 by using publicly available databases	– *HLA*-A*02:01 had a relatively lower capacity to present SARS-CoV-2 antigens – Increase of deaths caused by COVID-19 in *HLA*-A*02:01 group	Tomita et al., 2020
ABO blood group	Analysis of 8,582,968 SNPs and meta-analysis of the two case-control panels	– 3p21.31 gene cluster (*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6* and *XCR1*) is a genetic susceptibility *locus* in patients with COVID-19 with respiratory failure – Association of 3p21.31 at *locus* 9q34.2 (ABO *locus*)	Ellinghaus et al., 2020
ABO blood group	Analysis of ABO blood type in 2173 SARS-CoV-2 infected patients from China	– Significant higher risk of SARS-CoV-2 infection in blood group A individuals – Significant lower risk of SARS-CoV-2 infection disease in blood group O individuals	Zhao et al., 2020
CAT[h]*EHF*[i]	Analysis of genes regulated by these variants through *cis*-eQTL and *cis*-meQTL acting and bioinformatics analysis	– *EHF* rs286914 functionally regulates the expression of *CAT* via cis-eQTL acting. – *EHF* may as an intermediary to affect the binding efficiency of ACE2 to SARS-CoV-2 S protein through *CAT*, thereby affecting the susceptibility of COVID-19	Qian et al., 2021
CCR5[j]	Analysis of a new mutation CCR5Delta 32 in 416 SARS-CoV-2-positive infection survivors (164 asymptomatic and 252 symptomatic)	– Association of the highest number of CCR5Delta32 carriers in SARS-CoV-2-positive/COVID-19-asymptomatic subjects when compared to the SARS-CoV-2-positive/COVID-19-symptomatic patients – CCR5Delta32 I/D polymorphism may have the potential to predict the severity of SARS-CoV-2 infection	Hubacek et al., 2021
IFIH1[k]	Analysis of the *IFIH1* polymorphism, rs1990760 (C > T; aaA946T) in the epidemiology of SARS-CoV-2 infection in different populations	– T allele–carrying individuals may be more resistant to SARS-CoV-2 – Africans or African Americans with low allelic frequency of rs1990760 (T allele) are more vulnerable-risk groups than Caucasians and Indians	Maiti, 2020
IFITM3[l]	Analysis of the SNPs rs12252 and rs34481144 in the gene *IFITM3* in 239 SARS-CoV-2-positive and 253 SARS-CoV-2-negative patients	– Neither *IFITM3* rs12252 nor rs34481144 polymorphisms were related to SARS-CoV-2 infection risk or severity of COVID-19 – CAT plays a crucial intermediary role in binding effectiveness of *ACE2*, thereby affecting the susceptibility to COVID-19	Schönfelder et al., 2021

[a] *ACE2*: Angiotensin I converting enzyme 2.
[b] *CTSB*: Cathepsin B.
[c] *CTSL*: Cathepsin L.
[d] *TMPRSS2*: Transmembrane serine protease 2.
[e] *ACE1*: Angiotensin I converting enzyme.
[f] *CD26*: dipeptidil peptidase IV (DPPIV/CD26).
[g] *HLA*: Human leukocyte antigen.
[h] *CAT*: catalase.
[i] *EHF*: ETS homologous factor.
[j] *CCR5:* CC chemokine receptor 5.
[k] *IFIH1*: Interferon-induced helicase 1.
[l] *IFITM3*: Interferon-induced transmembrane protein 3.
[m] ChinaMAP: China metabolic analytics project (ChinaMAP).
[n] 1KGB: 1000 Genomes Project.
[o] HapMap3: International haplotype map project 3.
[p] eQTL: Expression quantitative trait *loci*.
[q] MHC: Major histocompatibility complex.

3p) are differentially expressed upon *in vitro* infection with SARS-CoV-2 in lung cancer cells. These authors observed low expression in lung epithelial cells for most of the miRNAs, which may be due to the lack of natural endogenous protection against infection of the lung epithelium and/or to selective tissue tropism of the virus due to miRNA tissue specificity according to the authors.

Another study has predicted 30 viral mature miRNA-like sequences to target 1367 host genes, affecting transcription, defense systems, metabolism and critical signaling cellular pathways, such as EGFR and WNT (Saçar-Demirci and Adan, 2020). Among the human miRNAs, 479 have been predicted to target SARS-CoV-2-related genes, binding to both the ORF and S region sequences of the virus. The main results of these studies are presented in Table 3 and the predicted SARS-CoV-2 gene targets of the human miRNAs presented above are illustrated in Fig. 1.

Several SARS-CoV-2 genome mutations, however, disrupt the binding sites of miRNAs and negatively impact their defense against viral modulation (Hosseini Rad Sm and McLellan, 2020). The suppression of RNAi silencing activity, a cell-intrinsic antiviral defense mechanism, is another viral escape strategy (Mu et al., 2020). Viral suppressors of RNAi activity have been reported in SARS-CoV and SARS-CoV-2 by the action of their nucleocapsid (N) protein, reversing the cellular silencing activity (Cui et al., 2015). As a result of these mechanisms, virus resistance against host defense mechanisms emerge and enable their survival in host cells (Mu et al., 2020).

5. MiRNA regulators of *ACE2* and *TMPRSS2* receptors

Among the human genes regulated by miRNAs upon SARS-CoV-2 infection are the *ACE2* and *TMPRSS2* genes. In viral infectious diseases, the regulation of *ACE2* by miRNAs has been reported by several authors. In a study evaluating the molecular basis of SARS infection, Mallick et al. (2009) reported downregulation of ACE2 expression and activation of inflammatory chemokines by the downregulation of miR-223 and miR-98, which are sequestered by the N and S protein targets. The authors also demonstrated that in bronchoalveolar stem cells, miR-17, miR-574-5p and miR-214 are sequestered by SARS-CoV to evade the immune system.

In acute lung injury (ALI), in which ACE2 treatment suppresses the severity of the disease by reducing the vascular tension and pulmonary accumulation of inflammatory cells, miR-4262 is significantly suppressed. In fact, *in vivo* administration of antisense miR-4262 in ALI mouse models decreases apoptosis of pulmonary cells (via BCL-2) and the severity of the disease (Bao et al., 2015). Interestingly, in a study of SARS-CoV-2-infected pulmonary cells, a correlation of miR-26a-5p and miR-29b-3p downregulation and increased levels of inflammatory markers, such as IL-4, IL-6 and IL-8, has been observed in postmortem lung biopsies of patients who developed acute respiratory failure (Centa et al., 2020). These findings demonstrate the association of miRNA expression alterations, endothelial dysfunction and the inflammatory response in patients with SARS-CoV-2 infection and ALI.

In patients with SARS-CoV-2, a miRNA target prediction analysis study has identified 1954 miRNAs regulating components of the *ACE2* interaction network (Wicik et al., 2020). This network also involves KEGG pathways related to heart-, lung-, nervous system tissue- and virus infection-related protein networks. Interestingly, hypertension is among the disease phenotypes associated with these networks, in which five miRNAs (miR-302c-5p, miR-1305, miR-587, miR-26b-5p and miR-27a-3p), including the previously described miR-27a-3p, are commonly involved.

Similar to other viral infections, SARS-CoV-2 infection may also affect the kidneys. ACE2 has also been shown to act as a proinflammatory mediator in acute kidney injuries or glomerular disorders associated with COVID-19 (Hardenberg and Luft, 2020). Widiasta et al. (2020) observed that several miRNAs targeting *ACE2*, including miR-18a, miR-125b, miR-143 and miR-181a, affect its expression in kidney tissue, and these miRNAs act as targeting genes, in addition to *ACE2*, associated with COVID-19 nephropathies. However, none of them have been evaluated in kidney samples of COVID-19 patients.

Alterations in the expression of miRNAs regulating the *TMPRSS2* gene have also been described. Prediction analysis of miRNAs targeting this gene has reported the presence of six SNPs influencing the miRNA target site and seed region (Paniri et al., 2020). In patients infected by SARS-CoV-2, other studies have suggested that the virus-encoded miR-147-3p acts as an enhancer of *TMPRSS2* expression to promote SARS-CoV-2 infection (Arisan et al., 2020).

Taken together, the data presented above illustrate the role of miRNAs in modulating *ACE2/TMPRSS2* expression in pulmonary and cardiovascular diseases caused by viral infections, including SARS-CoV-2. The variation in the expression of these proteins, by miRNA regulation via gene targets involved in critical immune and other host response-related processes, may be a genetic factor for the observed differences in the response of patients to SARS-CoV-2 infection and in the severity of COVID-19.

6. Therapeutic potential of miRNAs

Although miRNAs have been identified as potential biomarkers of infections caused by a range of pathogens and associated with differential outcomes in viral infections (Girardi et al., 2018), few studies have assessed their therapeutic potential. MiRNA drug target development has been focused mainly on the following two types of products: miRNA mimics and antagomiRs. Several potential miRNA therapies have reached phase I and phase II clinical trials, and some are in clinical development (Liu et al., 2020b; Alam and Lipovich, 2021). However, only two projects have targeted viral infectious diseases. These projects are based on antagomirs and were designed to sequester host miR-122 in patients with HCV infection. This host miRNA has been shown to inhibit an antiviral response by increasing viral RNA stability, ultimately leading to viral propagation. Both trials have entered phase II and shown promising effects against infection (Liu et al., 2020b). Other RNAi approaches for treating SARS infectious diseases have been developed. Of the 35 patents described in the Content Addressable Storage (CAS) content collection, only one uses a miRNA approach (Liu et al., 2020b).

Using the rich and valuable information obtained through *in silico* analysis, additional predictive viral-host miRNA interactions are expected to be identified, which may lead to the potential identification of new miRNA therapeutic targets. A 5′UTR analysis of highly expressed miRNAs reported in the lungs, the main target organ of SARS-CoV-2, has shown that miR-4507 and miR-638 can be considered for the development of antisense oligonucleotides, which would result in the inhibition of these miRNAs and consequently of viral replication (Baldassarre et al., 2020).

In summary, different strategies have highlighted the potential of miRNAs as therapeutic targets for COVID-19 through the design of antisense oligonucleotides or antagomiRs. As knowledge of host-pathogen interactions increases, novel viral-host miRNA interactions are expected to be identified, which may lead to the potential identification and development of new miRNA therapeutic strategies.

7. LncRNAs and SARS-CoV-2 infection

Another class of non-coding RNAs, lncRNAs, has also been associated with SARS-CoV-2 infection. LncRNAs are transcripts larger than 200 nucleotides in length that do not appear to have protein-coding potential, but some of them may produce functional small peptides. LncRNAs comprise a miscellaneous group of RNAs associated with multiple functions and that are dysregulated in multiple diseases (Cipolla et al., 2018).

Few studies have shown the association of lncRNAs with COVID-19 and their role in the SARS-CoV-2 antiviral host response (Table 3). Inflammatory cytokine storms have been described in patients infected with COVID-19, and IL-6 and the NLRP3 inflammasome are the primary

Table 3
Non-coding RNA-like sequences (miRNAs and lncRNAs) in SARS-CoV-2 and host genomes identified by *in silico* and experimental analysis.

ncRNA	Methodological approach	Main results	Reference
miR-1307-3p, miR-1468-5p, miR-3611, miR-3691-3p, miR-3934-3p, miR-5197, miR-8066a	Sequence analysis of miRNA sites in MERS, SARS, SARS-CoV-2, and cold virus (OC43 and 229E) from NCBI[a] and GISAID[b] databases	-Seven similar miRNAs (miR-1307-3p, miR-1468-5p, miR-3611, miR-3691-3p, miR-3934-3p, miR-5197, and miR-8066a) in the SARS-COV-2 genome from different geographic regions in association with virus pathogenicity and host response	Arisan et al., 2020
miR-15b-5p, miR-15a-5p, miR-30b-5p, miR-409-3p, miR-505-3p, miR-548c-5p, miR-548d-3p	Sequence analysis of 4 SARS isolates and 29 COVID-19 isolates from NCBI and GISAID databases	– 558 miRNAs identified – 315/558 miRNAs uniquely targeting COVID-19 patients genome – Seven miRNAs (miR-15b-5p, miR-15a-5p, miR-30b -5p, miR-409-3p, miR-505-3p, miR-548c-5p, and miR-548d-3p) with high target score in the COVID-19 patients genomes in association with age-related conditions/co-morbidities	Fulzele et al., 2020
miR-16-2-3p, miR-139-5p, miR-155-3p, miR-1275, let7a-3p	Sequence analysis of SARS-CoV, SARS-CoV-2 and MERS genomes	– 128 miRNAs associated with SARS-CoV-2 – 28/128 miRNAs common to SARS-CoV and 23/128 to MERS – Five miRNAs (miR-16-2-3p, miR-139 – 5p, miR-155-3p, miR-1275, and let7a-3p) differentially expressed in SARS-CoV-2 infected lung cancer cells (Calu-3)	Chow and Salmena, 2020
30 viral mature miRNA-like sequences	Sequence analysis of miRNA-like sequences in the SARS-CoV-2 genome from NCBI database and potential host-virus interactions	– 30 viral mature miRNA-like sequences predicted to target 1367 host genes – miRNAs affected transcription, defense systems, metabolism, and critical signaling cellular pathways, such as the EGFR[c] and WNT	Saçar-Demirci and Adan, 2020
miR-10b-5p, miR-16-5p, miR-26b-5p, miR-27a-3p, miR-124-3p, miR-200b-3p	- *In silico* miRNA target prediction analysis of *ACE2*[d] gene network and interaction with SARS-CoV-2 related	– 1954 miRNAs predicted to regulate *ACE2* gene network and also associated with KEGG[e]	Wicik et al., 2020

Table 3 (*continued*)

ncRNA	Methodological approach	Main results	Reference
miR-302c-5p, miR-587, miR-1305	diseases and mainaffected systems (heart, lung and nervous systems)	pathways related to heart, lung, nervous system tissues, and virus-infection – Nine miRNAs (miR-10b-5p, miR-16-5p, miR-26b-5p, miR-27a-3p, miR-124-3p, miR-200b-3p miR-302c-5p, miR-587, miR-1305) among the top ones regulating the *ACE2* network – 5/9 miRNAs (miR-26b-5p, miR-27a-3, miR-302c-5p, miR-587, and miR-1305) associated with hypertension	
miR-18a, miR-125b, miR-143, miR-181a	Review article-Prediction analysis of miRNAs targeting *ACE2*	– Four miRNAs (miR-18a, miR-125b, miR-143, and miR-181a) predicted to target *ACE2* and associated with COVID-19 nephropathies	Vidiasta et al., 2020
miR-127-3p, miR-153-3p, miR-204-5p, miR-211-5p, miR-448, miR-548c-3p, miR-593-3p, miR-1324, miR-4433b-3p,miR-4666b, miR-4685-3p, miR-4696 miR-4716-5p, miR-5011-3p, miR-5089, miR-6076, miR-6729-5p, miR-6797-3p, miR-6818-3p	Sequence analysis of *TMPRSS2*[f] from Ensembl, Gtex[g], ExPASY2[h], GEPIA[i], and CCLE[j] databases	– Alterations in the expression of miRNAs regulating the *TMPRSS2* gene. – Prediction analysis of miRNAs targeting this gene, showed the presence of six SNPs influencing miRNA target site and/or seed region of the miR-127-3p, miR-153-3p, miR-204-5p, miR-211-5p, miR-448, miR-548c-3p, miR-593-3p, miR-1324, miR-4433b-3p, miR-4666b,miR-4685-3p, miR-4696, miR-4716-5p,miR-5011-3p, miR-5089, miR-6076, miR-6729-5p,miR-6797-3p, and miR-6818-3p.	Paniri et al., 2020
miR-26a-5p, miR-29b-3p, miR-34a-5p	Clinical lung biopsies of SARS-CoV-2 patients with Acute lung injury (ALI) compared to biopsies of non-affected patients (qPCR)	– Three miRs (miR-26a-5p, miR-29b-3p and miR-34a-5p) down regulated in comparison to the controls – miR-26a-5p associated with endothelial dysfunction; induced increased expression of IL-6[k] and ICAM-1[l] – miR-29b-3p associated with	Centa et al., 2021

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Table 3 (*continued*)

ncRNA	Methodological approach	Main results	Reference
		endothelial dysfunction; induced expression of IL-4[m] and IL-8[n] – miR-34a-5p no association with inflammatory markers	
ANRIL, NEAT1, MALAT1, Gm4419, lincRNA-Cox2, XIST, EPS	Rat models, cell lines, clinical cases, C57BL/6 mice and BV2 mouse microglia	– ANRIL, NEAT1, MALAT1, Gm4419, lincRNA-Cox2 interfere in inflammasome formation by regulating NLRP3[o] levels. – XIST and EPS negatively regulated the activation of NLRP3 inflammasome	Menon and Hua, 2020
MALAT1, NEAT, MIR3142HG	Clinical cases analysis (lung tissue/bronchial cells)	– 3 lncRNAs (MALAT1, NEAT and MIR3142HG) with high expression in bronchial cells – MALAT1 induced IL-6 host immune response – NEAT associated with inflammasome formation – MIR3142HG-unknown function	Vishnubalaji et al., 2020
MALAT1, TSLNC8, NEAT, CAIF, HOTAIR	Human cell lines, lung injury rats and/or rat pulmonary microvascular endothelial cells	– Dysregulate IL-6 signaling pathway	Paniri and Akhavan-Niaki, 2020

[a] GISAID: Global Initiative on Sharing All Influenza Data.
[b] NCBI: National Center for Biotechnology Information.
[c] EGFR: Epidermal Growth Factor Receptor.
[d] *ACE2*: Angiotensin I converting enzyme 2.
[e] KEGG: Kyoto Encyclopedia of Genes and Genomes.
[f] *TMPRSS2*: Transmembrane serine protease 2.
[g] GEPIA: Original Research Interactive Analysis.
[h] ExPASY2: Expert protein analysis system 2.
[i] GTEx: Genotype-Tissue Expression.
[j] CCLE: Cancer cell line encyclopedia.
[k] *IL-6:* Interleukin-6.
[l] *ICAM-1*: Intercellular Adhesion Molecule 1.
[m] *IL-4*: Interleukin 4.
[n] *IL-8*: Interleukin 8.
[o] *NLRP3*: NLR Family Pyrin Domain Containing 3.

immune components in immune response stimulation upon pathogen infection. The TSLNC8, MALAT1, NEAT1, CAIF and HOTAIR lncRNAs may regulate IL-6 expression via several pathways, including the JAK/STAT, NF-κB, HIF-1α and MAPK pathways (Paniri, 2020b). In contrast, the ANRIL, NEAT1, XIST, Gm449, RGMB-AS1 and Cox2 lncRNAs have been implicated in inflammasome formation (Yu et al., 2018; Xue et al., 2019).

LncRNAs have also been predicted to play a role in innate immune responses through their association with interferon (IFN) mechanistic pathways. Whole transcriptome analysis of the host response to SARS-CoV in mouse strains has highlighted over 500 differentially expressed annotated lncRNAs, which clearly show an association with innate immune signaling and pathogenesis regulation through signal transducer and activator of transcription 1 (STAT1) (Peng et al., 2010). Vishnubalaji et al. (2020) reanalyzed transcriptome data from primary normal human bronchial epithelial cells (NHBEs) during SARS-CoV-2 infection and lung biopsies derived from COVID-19 patients. These authors observed activation of the IFN response in SARS-CoV-2, and they reported that several differentially expressed lncRNAs (195 downregulated and 155 upregulated) are associated with viral infection. This previous study highlights the need for an in depth investigation of the observed dysregulated lncRNAs and their role in mediating the IFN response.

LncRNAs, acting as competitive endogenous RNAs (ceRNAs), may also competitively occupy the shared binding sequences of miRNAs, thus sequestering the miRNAs and changing the expression of their downstream mRNA target genes (Ala, 2020). This mechanism has been associated with SARS-CoV-2-infected cells, including one miRNA (miR-124-3p), one mRNA (Ddx58), one lncRNA (Gm26917) and two circular RNAs (Ppp1r10 and C330019G07RiK), with a potential role in immune mechanisms (Peng et al., 2010). LncRNAs also interact with target mRNAs through base pairing to enhance or inhibit their translation (Fernandes et al., 2019). In this interaction mechanism, a comparison of RNA-seq data from samples of COVID-19 patients and healthy individuals has suggested that the PVT1 and HOTAIRM1 lncRNAs have a high affinity for binding to the virus genome and that these lncRNAs have a significant regulatory role during infection (Moazzam-Jazi et al., 2021). Of note, these interactions cover the ORF1ab gene and rarely span NSP5 or NSP6, excluding the sequence of the spike protein present in mRNA-based vaccines and avoiding side effects based on lncRNA interactions.

One of the main features of lncRNAs is their high specific expression profile. Recently, two studies on lncRNA expression in peripheral blood have utilized a gene panel to distinguish patients from controls and between patients with severe and nonsevere COVID-19 (Taheri et al., 2021). The combination of the transcript levels of VDR, CYP27B, SNHG6, SNHG16, Linc00511 and Linc00346 can differentiate patients from controls with high specificity (Taheri et al., 2021). Another lncRNA panel consisting of AC010904.2, AC012065.4, AL365203.2, AC010175.1, LINC00562, AC010536.1 and AP005671.1 presents a good differential ability between severe and nonsevere COVID-19 patients (Cheng et al., 2021).

Although still not fully explored, the role of lncRNAs in the cellular response to SARS-CoV-2 infection and their association with COVID-19 prognosis is promising. The understanding of the effects of their differential expression and mode of action will impact immunology and infectious diseases, such as COVID-19.

8. Conclusions

Extraordinary worldwide research and clinical efforts have been made to understand the complex mechanisms of SARS-CoV-2 infection. While there are still many mechanisms to be elucidated, these efforts have significantly contributed to the knowledge of the diverse and multiple cellular and immune factors that are associated with COVID-19 pathogenesis. The identification of variants of both virus and host genomes in addition to the regulatory role of non-coding RNAs has contributed to defining patient risk groups beyond those based on patients' age, clinical symptoms and types of comorbidities. These genetic factors highlight and illustrate the genome diversity of the virus isolates and individuals as well as their impact on the susceptibility to the disease, offering the possibility of changes in the clinical management of the infection by guiding treatment and reducing COVID-19 morbidity and mortality rates.

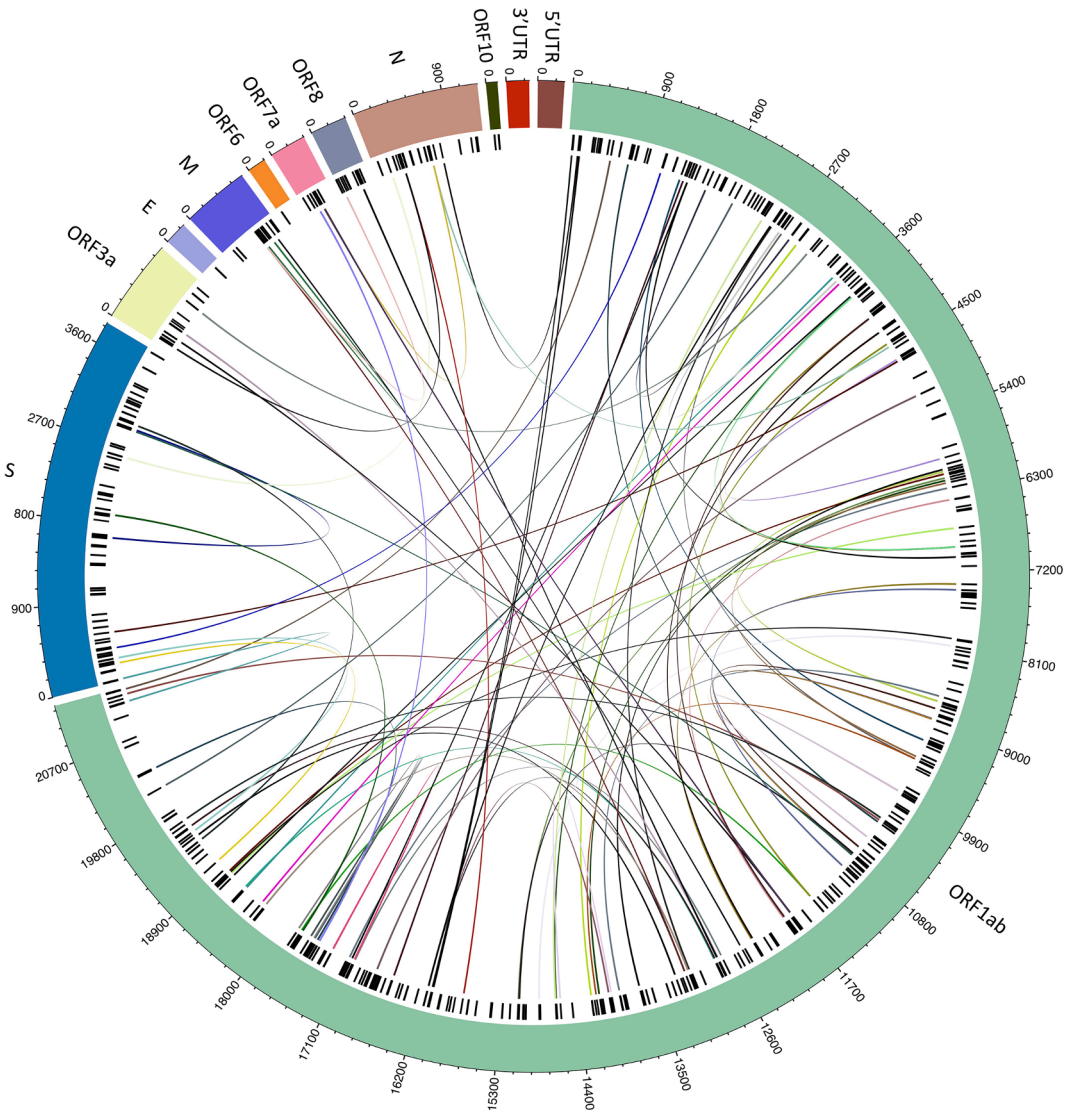

Fig. 1. Circle representation of predicted targets for human miRNAs in genes involved in the SARS-CoV 2 life cycle. Outer circle indicates the SARS-CoV-2 genome location (nt) and annotation. In the inner circle, black bars represent loci for human miRNAs. Connecting lines characterize human miRNAs that have multiple targets in the viral genome.

Declaration of Competing Interest

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

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Conflicts of interest/Competing interests

The authors declare no conflict of interest or competing of interests.

Appendix A. Supplementary data

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