REVIEW / ARTÍCULO DE REVISIÓN

Major epigenetic factors associated with the novel coronavirus disease-2019 (COVID-19) severity

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Abstract: The worldwide spread and high rate of viral transmission and related morbidity and mortality of Coronavirus disease-19 (COVID-19) is a crisis. Some epigenetic determinants predispose individuals to severe infection. Patients with prior chronic medical illnesses (hypertension, diabetes, lupus, and chronic obstructive lung disease) are highly susceptible to the infection. The aging and diabetes pandemic possibly exacerbate the COVID-19 or SARS-CoV-2 pandemic by enhancing COVID-19 associated comorbidities. COVID-19 utilizes several proteins for tackling the host immune response associated with enhancing comorbidities. The angiotensin-converting enzyme (ACE) is a significant receptor for SARS-CoV-2, which significantly expresses higher among individuals with comorbidities and under stress conditions. Patients with systemic lupus erythematosus are also prone to be susceptible to the disease. Viral infections cause a defect in the DNA methylation in lupus, causing further ACE2 hypomethylation and overexpression, leading to viral binding and cytokine storm and tissue damage during COVID-19 infection. The microRNAs (miRNAs) epigenetics regulations also play a critical role in the suppression of immune responses. Meanwhile, viral proteins interplays with the host cell are conferred primarily through TGF-β and HIF-1 signaling, endocytosis, autophagy, and Toll-like receptor signaling RIG-I signaling, Il-17 signaling, and fatty acid oxidation/degradation. Furthermore, the COVID19 patient's metabolic states determine the infection severity. Noticeably, ten human metabolic proteins, including SGTA, SPECC1, FGL2, PHB, STAT3, BCL2L1, CAV1, JUN, PPP1CA, and XPO1, interact with the SARSE-CoV-2. Interactions between SARSCoV's spike protein-containing lipid-rich membrane compartments and epigenetic modulations are considered targets to inhibit the viral infection. Therefore, it seems that epigenetics plays a substantial role in the COVID-19 severity. Future in-depth studies will be promising. Vaccine design, particularly regarding ACE viral receptor monoclonal antibodies, is a proposal alongside adhering to personal hygiene.

Key words: Coronavirus disease-19, epigenetics, severe respiratory disease.

Introduction

For fighting against every infection, a triangle including genetics, environment, and lifestyle is the primary determinant of triumph. The recent emergence and spread of novel *Coronavirus* disease known as COVID-19 or Severe Acute Respiratory Syndrome *Coronavirus*-2 (SARSE CoV-2, also coronavirus) in Wuhan in central China, has recently caused a pandemic scale of pneumonia in humans leading to concurrently and continuing high transmission, morbidity and mortality rat[1] *Coronavirus* subfamily is single-stranded positive-sense (+ssRNA) virus. The pandemic spread of novel coronavirus disease-19 (CoVID-19) in 2019-2020 originated from Wuhan, China, continues to affect human health and many life aspects and activities. The severity of infection increases with advancing age. Data suggests that very complex host-virus interplays occur during the SARS-CoV-2 infections (table1 and Figure 1).

Although the pathogenicity of SARSE-CoV-2 has not been entirely understood, extensive lung damage, enhanced infiltration of monocytes, macrophages, and neutrophils within the respiratory system and the blood storm of proinflammatory cytokines and chemokines are associated with the severity of infection[2,3]. Another mechanism of viral evasion includes delayed IFN type I transduction which stimulates the monocytes and macrophages and delays T-cells activation. Both the SARSE-CoV and SARSE-CoV-2 viruses bind to the angiotensin-converting enzyme receptor (ACE) via their spike protein receptor-binding domains which share 72% amino acid similarity[4,5]. Strikingly, the SARSE-CoV-2 domain has an incredibly higher receptor affinity. Higher expression of ACE among patients with comorbidities supposedly predisposes them to severe infection.

Moreover, it was stated that viral binding to the ACE downregulates its expression and leads to lower level biosynthesis of end-product vasodilator heptapeptide angiotensin 1-7. This, in turn, causes lung injury due to increased pulmonary vascular permeability. Another receptor for *Coronaviruses* includes a zinc peptidase known as aminopeptidase N (APN), which shares homology and membrane topological similarities with the ACE[4,6,7].

Those epigenetic factors mainly facilitating the viral attachment to host cells seem to enhance the death rate. These primarily include methylation or expression of angiotensin-converting enzyme 2 (ACE2), microRNAs regulation, metabolic conditions, individual behavior (such as smoking), and some environmental conditions (temperature and humidity)[37-39].

The genomic material released by its virus is mRNA, so it is prepared to stay translated into protein. In its genome range, its virus is complemented by using respecting 14 open reading frames (ORF), each of which encodes a variety concerning proteins, each structural yet non-structural, so move a function into its uplift so nicely as much virulence power. In its transformation section, the gene segments so encode non-structural polyproteins use this method to advance ORF1a yet ORF1b under production twins full-size overlapping polyproteins, pp1a and pp1ab utilizing contributing a ribosomal body shifting match[40] . The polyproteins are supplemented by using protea-

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nsps (range)	Functions	Ref.
nsp1 (1–180)	• The nsp1 is encoded by α-CoVs and β-CoVs but not by γ-CoVs and δ-CoVs • Blocks host cell translation • Cellular mRNA degradation • Chemokine Dysregulation • Highly divergent among CoVs • Inhibiting IFN signaling • Regulation of host and viral genes expression • Promotes cellular/host mRNA degradation • Potential virulence factor • Results in blocking the innate immune response Suppress of type I interferon • Suppress the host protein synthesis • Target for CoV vaccine development	**8-11**
nsp2 (181–818)	• Binds to prohibitin proteins • Dispensable for viral replication • Regulator of nsp3 gene function • Pivotal role in the viral life cycle • Viral infection	**12, 13**
nsp3 (819–2763)	• ADRP (ADP-ribose-1'-phosphate) activity promotes cytokine expression • Interacts with viral proteins and participates in viral assembly • Blocks host innate immune response • Blocking host innate immune response • Cleaves viral polyprotein • Key role in the replication/transcription of DNA • PLPro (papain-like proteinase) • PLPro/Deubiquitinase domain • Polypeptides cleaving • Promoting cytokine expression • The papain-like protease of Nsp3 as a target for therapy	**13-17**
nsp4 (2764–3263)	• Assembly of murine Coronavirus DMVs • Double-membrane vesicle (DMV) formation • Essential for viral multiplication by interaction with the nsp3 via H120&F121 • Potential transmembrane scaffold protein	**18, 19**
nsp5 (3264–3569)	• Cleaves viral polyprotein • Cysteine protease • Chymotrypsin-like protease (3CLpro) • Inhibiting IFN signaling • Main protease (Mpro) • Novel targets for non-active site inhibitors • Polypeptides cleaving	**20, 21**
nsp6 (3570–3859)	• Complex with nsp3 and 4: DMV formation • Potential transmembrane scaffold protein • Restricting autophagosome expansion	**22**
nsp7 (3860–3942)	• Cofactor with nsp8 and nsp12 • Complex with nsp8: primase • Hexadecameric complex with nsp8 • As a clamp for RNA polymerase	**21, 23, 24**

Table 1. Major *Coronavirus* non-structural proteins (nsps) and their pathogenicity capabilities.

nsp8 (3943–4140)	• Cofactor with nsp7 and nsp12 • Complex with nsp7: primase • Forms hexadecameric complex with nsp7 • May act as processivity clamp for RNA polymerase	**21, 25**
nsp9 (4141–4253)	• Dimerization and RNA binding • Replicase Protein • RNA binding protein	**26**
nsp10 (4254–4392)	• Cofactor for nsp16 and nsp14 • Complex with nsp14: replication fidelity • Enzymatic co-factor • Stimulates the ExoN and 2-O-MT via heterodimer forming • As the nsp14 and nsp16 scaffold protein	**27-29**
nsp11 (4393–5324)	• Endoribonuclease (EndoU) • Short peptide at the end of orf1a	**30, 31**
nsp12 (5325–5925)	• NiRAN, nidovirus RdRp-associated nucleotidyl transferase • Primer dependent RdRp • RNA-dependent RNA polymerase (RdRp)	**32, 33**
nsp13 (5926–6452)	• Exoribonuclease activity acting in a 3′ to 5′ direction and N7-guanine methyltransferase activity.	**34**
nsp14 (6453–6798)	• Mn(2+)-dependent endoribonuclease activity	**34**
nsp15 (6799–7096)	• Methyltransferase that mediates mRNA cap 2′-O-ribose methylation to the 5′-cap structure of viral mRNAs	**35**
nsp16 (4393-4405)	• **Avoiding MDA5 recognition and inhibit innate immunity regulation**	**21, 36**

Table 1. Major *Coronavirus* non-structural proteins (nsps) and their pathogenicity capabilities.

se enzymes, specifically papain-like proteases (PLpro), yet a serine kind Mpro (chymotrypsin-like protease (3CLpro)) protease as are encoded of nsp3 then nsp 5. Subsequently, burst occurs into pp1a yet pp1ab into non-structural proteins (nsps) 1–11 and 1–16. The nsps shed a vital role in deep approaches of viruses yet host cells, as shown in Table 1[21].

Angiotensin-converting enzyme as the CoVID-19 receptor

Several body compartments, such as respiratory and gastrointestinal systems, have cells that express the *ACE2* as the CoVID-19 receptor for its binding, entry (activation of the viral spike glycoprotein and *ACE2* C-terminal segment cleavage), replication, and shedding. Epigenetics surveys have suggested that the *ACE2* gene located on the X chromosome is regulated by DNA methylation[41-43]. It was postulated that the variability in D/I genotype distribution of the *ACE* gene is possibly associated with the variable prevalence of the COVID-19 infection[42].

Notably, methylation varies across tissue cell types, and at three CpGs (cg04013915, cg08559914, and cg03536816) was lowest in lung epithelial cells. This figure was significantly lower among females than males, which differs in the *ACE2* gene and protein expression and COVID-19 severity[44]. Interestingly, increased *ACE2* expression has been observed by staining lung tissue sections from patients with pulmonary hypertension. As the potential cause of *ACE2* gene expression, enzymes that modify histones (KDM5B, H3K27a, H3K4me1, and H3K4me3) are notable. However, significant differences in *ACE2* between racial groups, age groups, or gender groups were not verified in one study. Besides, smoking as an epigenome effector was not shown to have a role in COVID-19 infection risk. Also, *IL-6* and *INS* (encoding the insulin hormone) genes have been associated with significant comorbidities. NAD-dependent histone deacetylase Sirtuin 1 (SIRT1) can also epigenetically induce the *ACE* gene expression under stress conditions. Viral infections cause a defect in the DNA methylation in lupus disease, causing further *ACE2* gene hypomethylation and overexpression, leading to viral binding and cytokine storm and tissue damage COVID-19 infection[45,46]. The viral

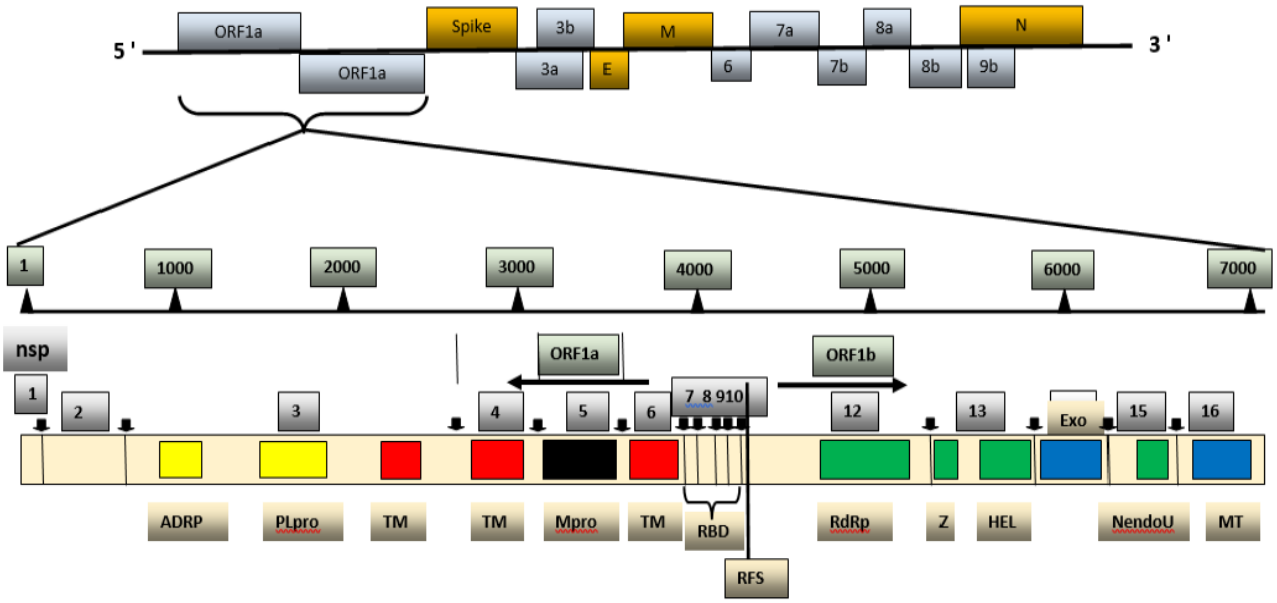

Figure 1. Genome and non-structural proteins of Severe Acute Respiratory Syndrome Coronavirus-2.

proteins exploit the host's genetic and epigenetic mediators, leading to viral evasion and determining disease pathophysiology (table1 and figure1). Besides, RAB1A gene was adequate for the COVID-19 infection development. Considering the ACE gene diffential expression, the age and sex of patients are also considered as risk factors for the COVID-19 infection[47].

Host and viral microRNAs epigenetic regulations

It has been revealed that epigenetics aspects of miRNA (small ncRNA molecules) mediated interactions with the host cells differ between SARSE-Cov and SARSE-Cov-2 (COVID-19). Hence, some viral miRNAs in a particular way affect several immune signaling pathways (IFN-I signaling, autophagy, etc.) that facilitate the prolonged latency. Moreover, COVID-19 modulates several critical cellular pathways resulting in the enhancement of anomalies in patients with comorbidities. The nucleocapsid protein from *Coronavirus* strain OC43 interacts with miR-9 and stimulates the NF-κB pathway. These findings are advantageous towards designing RNA therapeutics to mitigate the COVID-19 mediated comorbidities. Viral respiratory infections imposed by coronaviruses, influenza, adenovirus, rhinovirus, and RSV causes aberrant host miRNA expression mostly related to suppressing immune responses. Evidence has supposed that SARSE-Cov and SARSE-Cov-2 employ novel immune evasion strategies through utilizing host miRNA, but the exact mechanisms exerted by miRNA on the epigenetic interactions with the host have not been verified. It was hypothesized that genetic differences between SARSE-Cov and SARSE-Cov-2 and variations in binding to host miRNAs lead to differential pathogenesis[46].

Additionally, viral miRNAs differences and the fast mutation rate of SARSE-Cov2 in various regions have caused a higher pathogenicity rate. It was outlined that hsa-miR-20b-5p, hsa-miR-17-5p, and hsa-miR-323a-5p had anti-COVID-19 activities primarily targeting viral ORF1ab and S regions[44,48]. It is noteworthy that host miRNAs play a role like a double-edged sword and sometimes promote viral evasion, attachment, and replication. Patients suffering from underlying diseases (such as diabetes, cardiovascular diseases, and renal impairments) are more susceptible to SARS-CoV-2. It was revealed that host miRNA-mediated downregulated pathways disturb patients with the infection, making them more susceptible.

Viruses inflicting severe pulmonary illness can use three epigenetic-regulated approaches in the course of host-pathogen interaction: i. they execute affect host DNA methylation signatures then miRNAs regulating a cassette of genes underlying native yet adaptive antiviral responses; ii. those can encode because viral proteins up to expectation at once interact along with the host modified histones. Yet, iii. that may manipulate the host miRNA technology nuclear equipment in imitation of encoding viral non-canonical miRNA-like RNA fragments (v-miRNAs) regulating the viral life cycle or immune response[49]. Here, we center on epigenetic-sensitive mechanisms via who H5N1 and SARS-CoV-2 can also affect susceptibility in imitation of pulmonary sickness by interfering with both born yet adaptive immune responses into human beings, as shown in Figure 2.[50,51].

Mainly, T cells yet neutrophils execute bear deoxyribonucleic acid hypomethylation yet histone modifications, respectively, in COVID-19 patients. Otherwise, in vitro lung epithelial cells above H5N1 contamination can undergo adjustments of micro-ribonucleic sour taste (RNA) patterns yet histone tail marks, propulsion according to downregulation regarding antiviral defense. ACE, angiotensin-converting enzyme; AGO2, argonaute 2; CGI, CpG island; COVID-19, coronavirus disorder 2019; mRNA, messenger RNA; NET, neutrophil extracellular trap; NS1, non-structural protein 1; PCBP2, poly (RC)-binding protein 2; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory indication coronavirus 2; SLE, systemic lupus erythematosus.

Patients'behavior, nutrition, and metabolic conditions

COVID19 patient's metabolic states determine the infection severity. Noticeably, ten human proteins, including SGTA, SPECC1, PHB, BCL2L1, FGL2, STAT3, JUN, PPP1CA, CAV1, and XPO1 interact with the SARSE-CoV-2. Interactions between SARSCoV's spike protein with lipid-rich membrane compartments and epigenetic modulations are considered targets to inhibit the viral infection[52]. It was revealed that obesity is a risk factor for the SARSE-CoV-2 infection[53]. Noticeably, ten human metabolic proteins, including SGTA, SPECC1, PHB, BCL2L1, FGL2, STAT3, JUN, PPP1CA, CAV1, and XPO1 interact with the SARSE-CoV-2. Interactions between SARSCoV's spi-

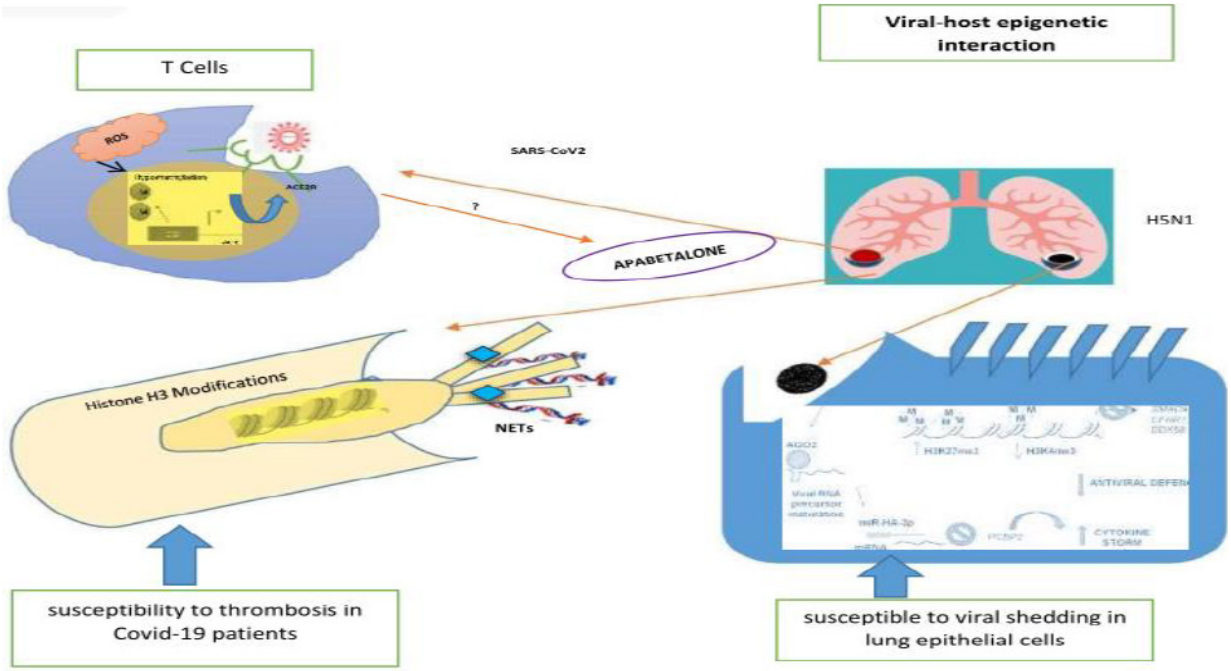

Figure 2. Viral–host epigenetic interactions. We illustrated that III putative cell-specific epigenetic-sensitive mechanisms using SARS-CoV-2 or H5N1 might also affect single sensitiveness according to severe pulmonary quintessential illness.

ke proteins, which have membranes rich in lipids components and epigenetic modulations, are considered targets to inhibit the viral infection. Some personal behaviors such as smoking or common personal behaviors that can reduce COVID-19 exposure are also notable, affecting the transmission, morbidity, and mortality rate[54,55].

Future perspectives

Owing to the lack of effective vaccination until now, investigations in this regard will be promising. Additionally, the application of lower toxic disinfectants and adherence to personal hygiene; particularly among individuals meeting healthcare and developing effective drugs, can be helpful towards reducing the burden of infection. More in-depth verifications regarding epigenetic factors and application inhibitors of the ACE and outcomes are also proposed.

Conclusions

Those epigenetic factors mainly facilitating the viral attachment to host cells seem to enhance the death rate. These primarily include methylation or expression of angiotensin-converting enzyme 2 (*ACE2*), microRNAs regulation, metabolic conditions, individual behavior (such as smoking), and some environmental conditions (temperature and humidity). The angiotensin-converting enzyme (*ACE*) is a significant receptor for SARS-CoV-2, which significantly expresses higher among individuals with comorbidities and under stress conditions. Patients with systemic lupus erythematosus are also prone to be susceptible to the disease. Viral infections cause a defect in the DNA methylation in lupus, causing further *ACE2* hypomethylation and overexpression, leading to viral binding and also cytokine storm and tissue damage during COVID-19 infection. The microRNAs (miRNAs) epigenetics regulations also play a critical role in the suppression of immune responses.

Meanwhile, viral proteins interplays with the host cell are conferred mainly through TGF-β and HIF-1 signaling, endocytosis, autophagy, and Toll-like receptor signaling RIG-I signaling, Il-17 signaling, and fatty acid oxidation/degradation. Furthermore, the COVID19 patient's metabolic states determine the infection severity. Noticeably, ten human metabolic proteins, including SGTA, SPECC1, PHB, BCL2L1, FGL2, STAT3, JUN, PPP1CA, CAV1, and XPO1 interact with the SARSE-CoV-2. Interactions between SARSCoV's spike structural proteins containing membranes rich in lipidic macromolecules and epigenetic modulations are considered targets to inhibit the viral infection. Therefore, it seems that epigenetics plays a substantial role in the COVID-19 severity. Future in-depth studies will be promising. Vaccine design, particularly regarding ACE viral receptor monoclonal antibodies, is a proposal alongside adhering to personal hygiene.

Conflict of interest

None to declare.

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Ohe authors wrote this study.

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