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REVIEW ARTICLE

Deciphering epigenetic(s) role in modulating susceptibility to and severity of COVID-19 infection and/or outcome: a systematic rapid review

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Abstract

COVID-19 pandemic waves hitting worldwide result in drastic postinfection complications with interindividual variations, which raised the question for the cause of these observed variations. This urged to think "the impact of environment-affected genes"? In an attempt to unravel the impact of environment-affected genes, a systematic rapid review was conducted to study "the impact of host or viral epigenetic modulation on COVID-19 infection susceptibility and/or outcome." Electronic databases including Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar, and other databases were searched. The search strings included "COVID-19" OR "SARS-CoV-2" AND (Epigenetics'). Articles with randomized clinical trials (RCTs) and observational study designs, conducted on humans and available in the English language, were selected, with respect to "The interplay between the SARS-CoV-2 virus and Epigenetics" published from 2020 to February 2021 (but not limited to 2020, being expanded to 2015). Database search yielded 1330 articles; after screening, exclusion, and further filtrations, 51 articles were included. Susceptibility to COVID-19 infection is related to the viral-microRNAs (miRNAs) which alter virulence of the transmitted SARS-CoV-2 strains and impact host-miRNA-related innate immunity. Host-DNA methylation and/or chromatin remodeling may be implicated in severe cytokine storm that can ultimately results in fatal outcome.

Keywords Coronavirus · Epigenetics · MicroRNA · LncRNA · DNA methylation · Histone modification · Chromatin remodeling

Introduction

Problem

The molecular mechanisms underlying severe acute respiratory syndrome COVID virus-2 (SARS-CoV-2) pathogenesis are not yet fully elucidated, with an urgent need to design an effective therapeutic regimen against the CoV-2 pandemic that started November 2019 in China. Therefore, research is still going to unravel the pandemic molecular pathogenesis and find candidate effective therapeutic agents.

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Problem definition

In an attempt to define and explain the interindividual difference in response to infection as well as variation in reaction to infection, several factors need to be defined. These factors may be either related to the virus or related to the host.

The scope of the current systematic rapid review (SRR) is to point out the epigenetic factors that may alter the viability and transmissibility of the CoV-2 strain (Samaddar et al. 2020); and to address "gene expression alteration" arising from either chromatin structure modulation or posttranscriptional and/or posttranslational activity by protein-RNA interaction (Schäfer and Baric 2017).

The *epigenetic landscape* tends to contribute, first, to variation in the host susceptibility to SARS-CoV-2 infection and, second, to the host-pathological features and/or severity of symptoms, where SARS-CoVs could epigenetically antagonize host-cell–signaling and sensing components, in order to facilitate viral replication and drive pathogenesis together with

bypassing the host-induced innate immunity and/or the host-antiviral protection programs (Chlamydas et al. 2020). Besides, the host-pathogen interaction, witnessed in COVID-19-infected cases, results in striking variations in mortality rates across different geographical regions worldwide (Liu et al. 2020).

Aim

Summarizing the available knowledge regarding "the impact of epigenetics on the COVID-19 infection susceptibility, severity, and/or outcome." This, secondly, would hold a promise to personalized/precision medicine (PM) for better, hopefully successful, future treatment options, via proper identification and understanding of the host epigenetics.

Objectives

The current SRR was conducted to answer the following questions: (1) What are the host-epigenetic modifications that are associated with susceptibility and severity of COVID-19 infection? And how does SARS-CoV-2-epigenome influence host-infection susceptibility? (2) What is the role of epigenetics in modulating SARS-CoV-2 infection and/or its mutated forms in humans? (3) What is the value/influence of such epigenetic modification(s) on postinfection prognosis, complications, and/or outcome?

Methods

Design

Type of the review

Diagnostic, epidemiologic, prognostic.

PROSPERO registration #: CRD42021229133, was done on 8 January 2021.

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021229133

Searched electronic databases

The searched electronic databases were PubMed, ScienceDirect, Google Scholar, SCOPUS, Embase, CINAHL, SciELO, BVS, CAPES, LILACS, EBSCO, EMBASE, the Cochrane Library, and the grey literature search including the National Human Genome Research Institute (https://www.genome.gov/), WHO databases, and CDC. All records retrieved from database searches were downloaded locally and managed using the Mendeley X86 software facilities.

Study selection

Performed by two investigators independently with any disagreements being resolved by either the senior investigator or the chief investigator. Titles and abstracts selected for eligibility by two investigators from the studies retrieved during the searches and those identified meeting the inclusion criteria were chosen for use in the review by two authors and rechecked by another two authors, and then all investigators agreed for them. Any duplicates were removed using Mendeley X86 (Mendeley Desktop 1.19.8, by Mendeley Ltd.). Selected data was summarized using an Excel spreadsheet, full-text articles or reports which do not meet the inclusion criteria were excluded, and the reason(s) for exclusion are provided in the PRISMA Flowchart (Fig. 1). Moreover, the full texts of potentially eligible studies (51) were retrieved and evaluated independently for eligibility by both the senior and the chief investigators.

Data extracted included specific details about the condition, context, population, and study methods of significance to the review question(s) and specific objectives. PRISMA guidelines (Liberati et al. 2009) for systematic review presentation were followed.

Data extraction/synthesis is summarized in Tables 1, 2, 3, and 4 which include all epigenetics that were found to be associated with COVID-19, with no restrictions regarding country, race, gender, or age, and were classified into different epigenetics and the corresponding significance in relation to infection.

Results

Figure 1 outlines the PRISMA flowchart for the selection process, where a total of 2332 articles were found after searching for different databases. Duplicates (1002) found by Mendeley X86 were excluded. After title and abstract screening of the 1330 papers included, 1278 articles were found irrelevant (reasons are stated in the chart). Total eligible articles are 51.

Tables 1, 2, 3, and 4 summarizes the epigenetics landscape in SARA-CoV-2 infection, describing the association of various epigenetic factor(s) with different aspects of SARS-CoV-2 infection, namely, virus entrance into the host cell, viral replication, infection severity, postinfection complications as either cardiovascular (CV), pulmonary complications, or cytokine storm (CS) and more.

Figure 2 entitles the CoV-2 host-immune escaping mechanism(s) resulting in silent viral infection and fatal CS.

Figure 3 illustrates the CoV-2 infection-outcome regulatory triangle system consisting of the host, virus, and epigenetic target(s).

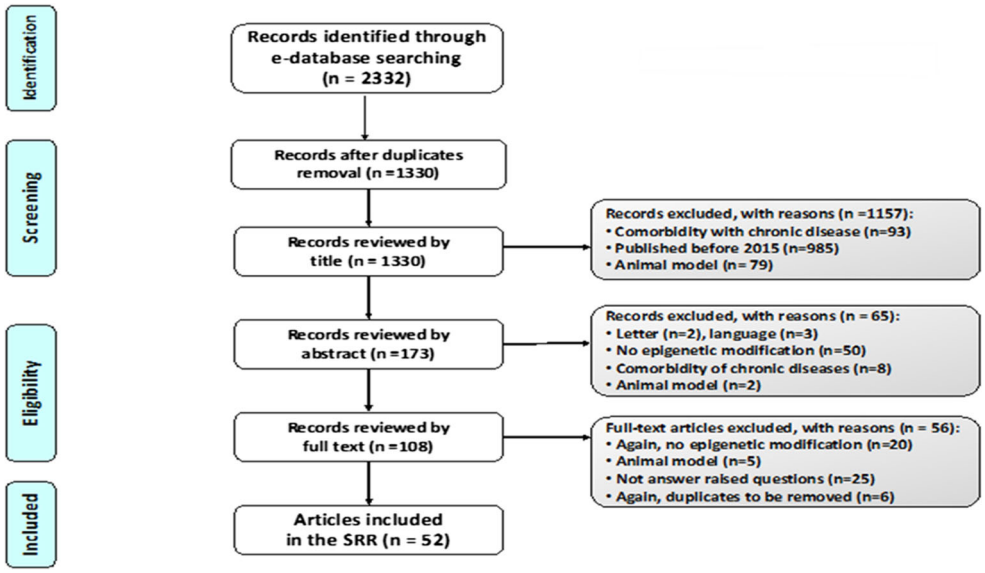

Fig. 1 PRISMA Flowchart

Figure 4 collectively highlights the epigenetic modulation(s) to address "gene expression alteration" as molecular mechanisms of SARS-CoV-2 pathogenesis.

Discussion

Epigenetic modifications

Small nonprotein-coding RNAs (ncRNAs)

ncRNAs comprise RNA molecules that do not encode a protein but regulate gene expression at multiple levels, including RNA splicing, editing, chromatin structure, and transcription (Canatan 2020). The ncRNA landscape of host cells could affect their vulnerability to viral infection and have a pivotal role in the cellular innate immune response against viruses (Henzinger et al. 2020).

MicroRNAs (miRNAs)

miRNAs are 19–23 nucleotides RNAs that regulate posttranscriptional silencing via targeting the messenger RNAs (mRNAs) 3′ untranslated region (3′UTR) (Canatan 2020). miRNAs regulate the expression of genes involved in various cellular processes and have, recently, emerged as critical modulators of viral infections (Henzinger et al. 2020; Meng et al. 2020).

In addition, viral-miRNAs can function as posttranscriptional gene regulators to both the host and viral genes (Pradhan et al. 2020). Understanding these processes holds a promise for the use of miRNAs as diagnostic or prognostic markers. Studying epigenetics to pave the road for finding the potential viral-miRNA-based treatments targets (epi-drugs) for successful personalized SARS-CoV-2 treatment (Abu-Izneid et al. 2020) is the future for implementing sustainable development goals (SDGs Vision 2030) and PM for good health (SDG #3) with minimal medications use, minimal side effects, and better environmental saving.

Role of miRNAs towards viral invasion, viral replication, pathogenies, and cellular response-to-viral infection

This includes two axes either the host or the viral epigenetics.

Host miRNAs

SARS-CoV-2 utilizes its spike (S) protein to mediate cell invasion. Human miRNAs, namely hsa-miR-8066, hsa-miR-5197-3p, and hsa-miR-3934-3p, were found to regulate the viral S protein synthesis (Abedi et al. 2020), which is also targeted by hsa-miR-98-5p in bronchoalveolar stem cells (Beidas and Chehadeh 2018). Moreover, host miRNAs regulate the expression of the most crucial proteins involved in SARS-CoV-2 cell invasion including human angiotensin-converting enzyme2 (ACE2), type II transmembrane serine protease 2 (TMPRSS2), and possibly a disintegrin and metalloproteinase domain 17 (ADAM17) and furin (Pontecorvi et al. 2020). ACE2 enables SARS-CoV-2 entry into host cells, being the receptor for the viral S protein cells attachment (Crimi et al. 2020; Shang et al. 2020). Other co-receptors required to complete the invasion process include TMPRSS2, which catalyzes cleavage and activation of the S protein. However, furin and ADAM17 are involved in membrane fusion (Shang et al. 2020). It was found that miR-421 and miR-143 decrease the expression of ACE2 (Ragia and

Table 1 Epigenetic noncoding RNA landscape in SARS-CoV-2 infection

Epigenetic factor		Significance	References
Noncoding RNAs	hsa-let-7e/hsa-mir-125a and hsa-mir-141/hsa-miR-200	Affect ACE2/TMPRSS2 expression	Henzinger et al. (2020)
	hsa-let-7a, hsa-miR101, hsa-miR125a-5p, hsa-miR126, 222, 23b, 378, 380-5 and hsamiR-98	Diagnostic biomarkers that may determine the occurrence and possible severity of the infection	Abu-Izneid et al. (2020)
	hsa-miR-27b	Hypothesized to have a specific role in defense against SARS-CoV-2 in the Indian population	Abedi et al. (2020)
	miR-376a-3p, miR-10a-5p, miR-548av-5p and miR-99b-5p	Host miRNA sponges	
	miRNA MD3-3P	Target and inhibit the *p53* gene	
	miR15b-5p, miR15a-5p, miR197-5p, miR548c-5p, miR548d-5p, miR409-3p, miR30b-5p, miR505-3p	Involved in blocking viral replication	
	hsa-miR-8066, hsa-miR-5197-3p, and hsa-miR-3934-3p	Regulate the synthesis of the viral Spike S protein	
	hsa-miR-1468-5p	Mediate cardiac tissue damage	
	miRNA-320a	Downregulates GLUT1 (*SLC2A1* gene)	
	miRNA-1-5p, miRNA-2-5p, miRNA-3-5p, miRNA-4-5p, miRNA-5-5p, and miRNA-6-5p	Involved directly/indirectly in the immune response upregulation and the pathway of chemokine signaling	
	miRNA 66-3p	Targets TNF-alpha	
	miRNA147-3p	Increased *TMPRSS2* gene expression in the gut and may be associated with the gastrointestinal symptoms of COVID-19	
	hsa-miR-8066 and hsa-miR-5197-3p	Involved with mucin-type-O-glycan synthesis	
	hsa- miR-98-5p	Targets viral S protein in bronchoalveolar stem cells	Beidas and Chehadeh (2018)
	miR-145 let-7, miR-145, and miR-222	Regulators of ADAM-17 expression	Pontecorvi et al. (2020)
	miR-20b, miR-19a, miR-19b, and miR-106a	Reregulate Furin activity	
	miR-421 and miR-143	Decrease the expression of ACE2	Ragia and Manolopoulos (2020)
	hsa-mir-9-5p	Targets 3′ UTR of ACE2	Khan and Islam (2020)
	hsa-mir-27b-3p	Plays a regulatory role in ACE2 signaling	
	hsa-miR-7849-3p, hsa-miR-7849-3p, hsa-miR-7849-3p, and hsa-miR-7849-3p	Regulate TMPRSS2 gene expression	Zarubin et al. (2020)
	hsa-miR-17-5p, hsa-miR-20b-5p, and hsa-miR-323a-5p	Antiviral activity; targeting pathways involved in suppression of viral entry, viral replication, and translation mechanisms	Khan et al. (2020)
	miRNA 197-5p	Implicated in cardiovascular complications post CoV-2	de Sanctis et al. (2020)
	miRNA-8066	Induce pro-inflammatory cytokines synthesis	
	miRNA (8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p, 1468-5p)	Modulate cell response and facilitate SARS-CoV2 infection	
	miR-574-5p, miR-214, miR-17, miR-98, miR-223, miR-148a	Mediating immunity	Hosseini Rad and McLellan- (2020)
	hsa-let-7a, hsa-miR101, hsa-miR125a-5p, hsa-miR126, hsa-miR222, hsa-miR23b, hsa-miR378, hsa-miR380-5, and hsa-miR98	Potentially target SARS-CoV-2, where hsa-miR-27b is hypothesized to have a specific defensive role against SARS-CoV-2 in the Indian population	Samaddar et al. (2020), Sardar et al. (2020)
	miR-320a, miR-3188, miR-3661, miR-217, miR-421, miR-429, and miR-421	Involved in the deregulation of pathways involved in the acute lung injury post-CoV-2 infection	Islam and Khan (2020)

Manolopoulos 2020). hsa-miR-9-5p targets 3′ UTR of ACE2, and hsa-miR-27b-3p plays a regulatory role during ACE2 signaling (Khan and Islam 2020). The miRNAs hsa-let-7e/hsa-mir-125a and hsa-mir-141/hsa-miR-200 can affect ACE2/TMPRSS2 expression, and their Jardin transcription was found to be repressed by lysine-specific demethylase 5B and Jumonji/ARID domain-containing protein 1B (JARID1B) (Abedi et al. 2020). miR-20b, miR-19a, miR-19b, and miR-106a can posttranscriptionally regulate furin expression (Pontecorvi et al. 2020). Moreover, TMPRSS2

Table 2 Epigenetic DNA methylation landscape in SARS-CoV-2 infection

Epigenetic factor		Significance	References
DNA methylation	TMPRSS2 methylation	Reduces S protein priming	Henzinger et al. (2020)
	Hypomethylation at the CpG site	Increased expression of *ACE2* gene	Franzen et al. (2020)
	Methylation of adenine of mRNA molecules in position 6 (N6-methyladenosine, m6A)	Alters mRNA stability of cellular and viral transcripts, affecting their translation efficiency and RNA-protein interaction	Choudhary et al. (2020)
	Demethylation of IFN-regulated genes, NF-$_k$B, and main cytokine genes	Enhances the expression of pro-inflammatory cytokines and chemokines, increasing cytokine storms incidence	El Baba and Herbein (2020)

Table 4 Epigenetic chromatin remodeling landscape in SARS-CoV-2 infection

Epigenetic factor		Significance	References
Chromatin remodeling	SARS-COV-2-induced repression of ACE2 via chromatin remodeling	Alters the activity of gene regulatory regions in the lung (PIR, CA5B, and VSP13C)	Fadason et al. (2020)
	Chromatin remodeling in CD14+ monocytes	Affect the severity of symptoms and provide potential prognostic markers for COVID-19 subjects	Giroux et al. (2020)

gene expression was shown to be regulated by hsa-miR-7849-3p, hsa-miR-7849-3p, hsa-miR-7849-3p, and hsa-miR-7849-3p (Zarubin et al. 2020). miR-145 let-7, miR-145, and miR-222 are implicated as regulators of ADAM-17 expression (Pontecorvi et al. 2020). On the other hand, miR-145 was found to be upregulated by vitamin D, which might explain COVID-19 severe progression in patients with vitamin D deficiency (Daneshkhah et al. 2020), as summarized in Table 1.

In addition to cell invasion, miRNA-mediated interactions between the host and the SARS-CoV-2 virus have several implications in terms of *disease complexity*. During viral infection, host-cell miRNAs bind to viral mRNAs resulting in

Table 3 Epigenetic histone modification landscape in SARS-CoV-2 infection

Epigenetic factor		Significance	References
Histone modifications	Methylation of H3K4 at the *ACE2* gene promoter	Affects ACE2 expression	Chlamydas et al. (2020)
	High level of repressive histone marks	Reduction of IL-12 and IL-1β, contributing to CoV-2 severity	
	H3K4me3	Regulates TLRs involved in the innate immune system	El Baba and Herbein (2020)
	H3K9ac, H3K36ac, and H4K5ac	Suppression of IL-8 and TNF-alpha levels in response to CoV	
	H3K4me1, H3K4me3, H3K27Ac in the *ACE2* gene	Increased ACE2 expression	Pinto et al. (2020)
	NAD-dependent histone deacetylase sirtuin 1		
	Acetylation and hypermethylation of histone marks	Upregulation of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, TNF-5-007) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10) contributing to cytokine storms	Ovsyannikova et al. (2020)
	H3 modifications	NET in organ damage and mortality in COVID-19 patients	McCracken et al. (2020)
	G9a, a histone methyltransferase	Increased inflammation and T-cell function impairment or lymphopenia	Wang et al. (2020)
	H3K27 acetylation	Expression of inflammation-associated genes	Li et al. (2020)

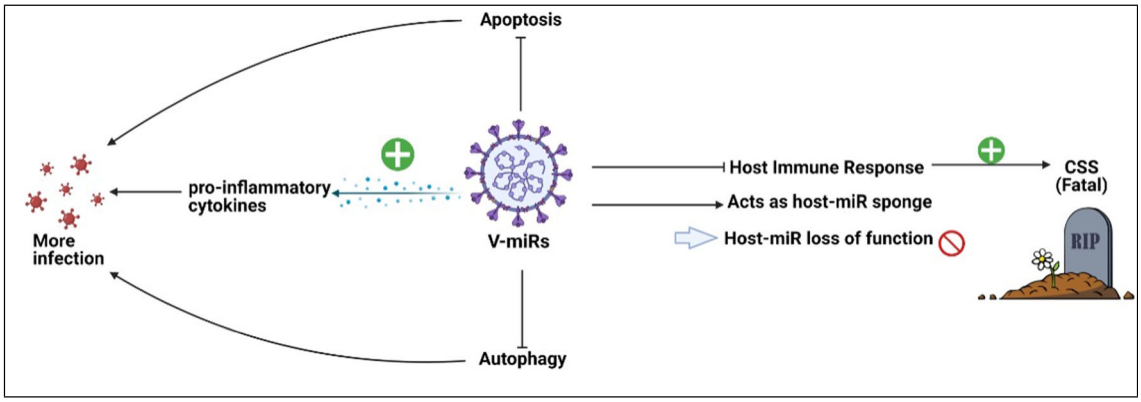

Fig. 2 SARS-CoV-2 host-immune–escaping mechanism(s) without symptoms of COVID-19 infection

either inhibition of viral genome translation and, hence, inhibition of viral replication or viral-RNA stabilization rendering the virus resistant to the host immune response (Abu-Izneid et al. 2020). *In silico* assessment has identified 873 miRNAs that could target SAR-CoV-2 genes (Srivastava et al. 2020). Those identified 873 miRNAs could be associated with the modulation of the innate and adaptive host immune response to viral infection (Abu-Izneid et al. 2020), an impact that may be either direct or indirect via influencing the interferon (IFN)-alpha/beta signaling.

On the one hand, several host miRNAs nowadays are reported to exhibit experimentally evidenced *antiviral activities*, as hsa-miR-17-5p, hsa-miR-20b-5p, and hsa-miR-323a-5p, via suppression of the virus entry to cells (such as platelet-derived growth factor receptor-like, PI3K-Akt, and cadherin signaling) or suppression of viral replication and suppression of viral proteins translation mechanisms (such as p38, mitogen-activated protein kinase (MAPK), and focal adhesion kinase (FAK) signaling) (Khan et al. 2020).

Bioinformatic assessments revealed host miRs (15b-5p, 15a-5p, 197-5p, 548c-5p, 548d-5p, 409-3p, 30b-5p, 505-3p) that may be involved in blocking viral replication (de Sanctis et al. 2020). Some miRNAs are hypothesized to fight SARS-CoV-2 efficiently by triggering a defensive response and reducing host cell apoptosis (Abedi et al. 2020). Hosseini et al. identified seven miRNA targets in the SARS-CoV-2 genome that mediates immunity (miR-574-5p, miR-214, miR-17, miR-98, miR-223, and miR-148a) (Hosseini Rad and McLellan 2020). Sardar et al. found 51 miRNAs interacting with 77 transcription factors that are involved in the host-antiviral activity modulation (Sardar et al. 2020).

On the other hand, host miRNAs can also act as double-sided coin, where the interplay between host miRNAs and SARS-CoV-2 can promote viral pathogenesis by deregulating the major antiviral immune-signaling pathways (Sarma et al. 2020; Khan et al. 2020), as shown in Fig. 2, which illustrates CoV-2 host-immune escaping mechanism(s), where host-miRNAs are being sponged by the viral-miRNAs to facilitate viral-directed immune evasion, which includes IFN-gamma,

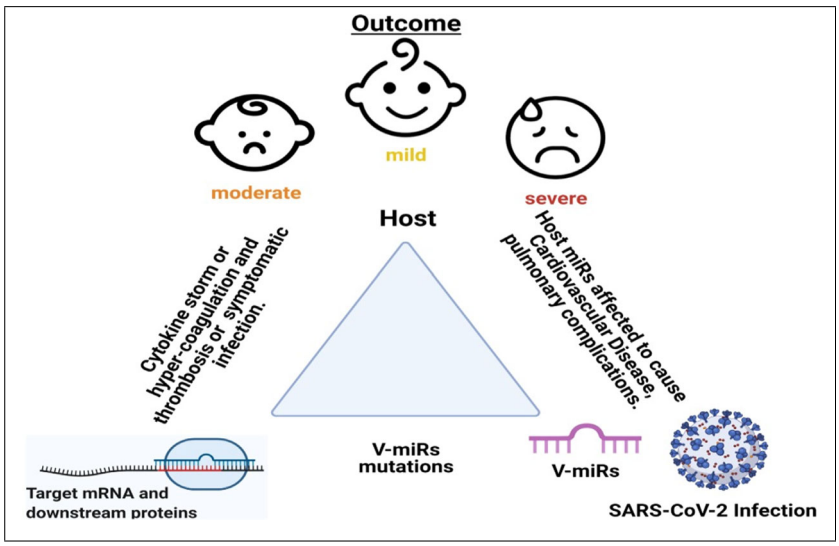

Fig. 3 SARS-CoV-2 infection outcome regulatory triangle system. The role of miRNAs in SARS-CoV-2 prognosis; host miRNAs, viral-encoded miRNAs, and both mRNA and miRNA targets, contributing to the infection outcome to be either moderate, severe, or mild

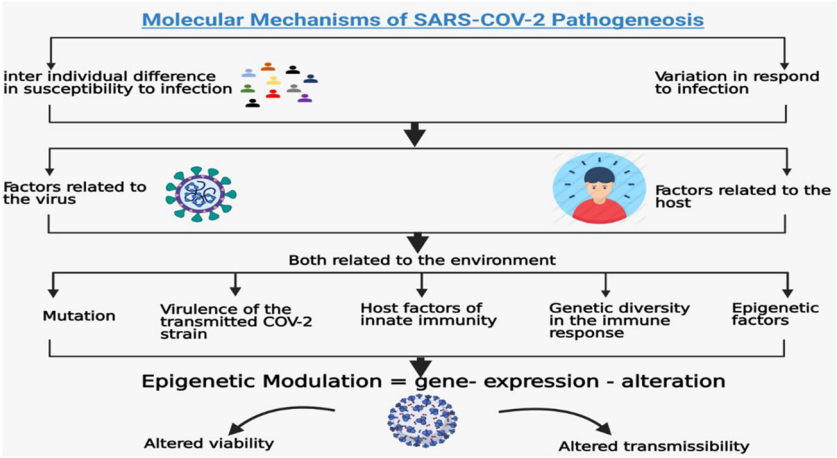

Fig. 4 Epigenetic modulation, namely, gene expression alteration as molecular mechanisms of CoV-2 pathogenesis

transforming growth factor-beta (TGF-beta), interleukin (IL), insulin-like growth factor-1 (IGF-1), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Sarma et al. 2020; Khan et al. 2020). During SARS-CoV-2 infection, host-miRNAs may downregulate different toll-like receptors (TLRs) signaling, essential for the host antiviral mechanisms development. Several additional signaling pathways including tumor necrosis factor receptor-associated factor 6 (TRAF6), sphingosine 1-phosphate receptor 1 (S1P1), estrogen receptor, and protease-activated receptor (PAR) are inhibited by viral-miRNAs resulting, unfortunately, in a decline of the host-antiviral defense (Abu-Izneid et al. 2020; Khan et al. 2020; Sardar et al. 2020). Both cellular miRNAs and viral-encoded miRNAs induced post-SARS-CoV-2 infection were found to target cytokine-signaling involved during the immune response, with a net result of an increased viral pathogenesis (Khan et al. 2020) (Fig. 2).

Nucleocapsid protein of the human *Betacoronavirus* 1 OC43 (HCoV-OC43), which enters its host cell by binding to the N-acetyl-9-O-acetylneuraminic acid receptor, binds to hsa-miR-9-5p, with subsequent activation of the transcription factor nuclear factor-kappa B cell (NF-κB) and more alteration of the innate immune response (Beidas and Chehadeh 2018).

Additionally, studies revealed the promising possibility of using miRNAs as COVID-19 diagnostic biomarkers as well as to reflect infection severity (Abedi et al. 2020), including hsa-let-7a, hsa-miR101, hsa-miR125a-5p, hsa-miR126, hsa-miR222, hsa-miR23b, hsa-miR378, hsa-miR380-5, and has-miR98 (Abu-Izneid et al. 2020). The host-miRNAs involved in the nuclear machinery can be manipulated to encode specific viral-miRNA-like-RNA fragments to control the virus life cycle together with the host immune response (Mishra et al. 2020).

Viral miRNAs and SARS-CoV-2 miRNAs

Viral miRNAs are the ugly face of the currently studied miRNAs in relation to COVID-19 infection. Viral miRNAs can regulate the host-gene expression (miRNA targets), cellular proliferation, and stress-related genes. Therefore, SARS-CoV-2 can interfere with human innate and adaptive immunity via the viral epigenetic-sensitive machinery (Crimi et al. 2020). SARS-CoV-2-encoded miRNA interactions with the host-miRNA can target autophagy pathways, IFN-1/wingless-related integration site/mechanistic target of rapamycin, previously referred to as the mammalian target of rapamycin (IFN-1/Wnt/mTOR) signaling and Ca^{2+} signaling pathway (Khan et al. 2020) and, again, activate pro-inflammatory cytokines via an increased NF-κB activity (Identify et al. 2020). Additionally, viral miRNAs 8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p, and 1468-5p may modulate host-cell response and facilitate SARS-CoV-2 infection (de Sanctis et al. 2020; Identify et al. 2020).

An altered host-miRNA expression may be involved in the CS occurring post-SARS-CoV-2 infection, by triggering the cascade of chemokine signaling through targeting C-X-C chemokine ligand 16 (CXCL16) and the putative enhancer region of arrestin beta-2 leading to lung inflammation (Abedi et al. 2020). miR-66-3p was also found to target tumor necrosis factor-alpha (TNF-alpha) in the spleen (Abedi et al. 2020). CS, observed in severe infected cases, could be attributed to miR-8066 that activates NF-κB-mediated TLR-8 expression and, hence, induces more pro-inflammatory cytokine synthesis (de Sanctis et al. 2020).

In addition, SARS-CoV-2 can evade the host's immune surveillance by utilizing its miRNAs to target a myriad of significant functions and pathways involved in the host immune response, such as MAPK signaling, T-cell–mediated immunity, fibroblast growth factor (FGF) receptor binding

and vascular endothelial growth factor (VEGF) signaling, ErbB signaling (Abedi et al. 2020), and erythroblastic leukemia viral oncogene type I receptor family epidermal growth factor (EGF) receptor (EGFR), suggesting a "CoV-2 host-immune–escaping mechanism(s)" without any symptoms of COVID-19 infection (Fig. 2). SARS-CoV-2 can release its v-miRNAs into the host cells to overturn and neutralize host-cell apoptosis or autophagy, counteracting the defense mechanism employed by the host via apoptosis/autophagy balance to reduce and/or localize the viral spread (Crimi et al. 2020).

Viral miRNA can escape the host-immune cell degradative action, by suppressing certain mRNA de-adenylase transcription complex(es) as the carbon catabolite repression—negative on TATA-less subunit 4 (CCR4-Not; CNot4), CNot6 ligand, and CNot10 subunits (Abedi et al. 2020).

Moreover, SARS-CoV-2 miRNAs can inhibit the host production of antiviral proteins, increasing the susceptibility of cells to SARS-CoV-2 infection via affecting Janus kinase (JAK) 1 and 2 and signal transducer and activator of transcription (STAT) 3, 4, 5B, and 6 and upregulating the suppressor of cytokine signaling (*SOCS*) cellular genes. Viral miRNAs can prevent RNA polymerase II attachment to the host gene promoters at the initiation stage or by targeting transcription regulators involved in the transcription machinery (de Sanctis et al. 2020) (Fig. 2).

Role of miRNAs in SARS-CoV-2 prognosis

Host miRNAs, viral-encoded miRNAs, and both mRNA and miRNA targets, together form *a regulatory triangle system* (Khan et al. 2020) (Fig. 3), between both the host and virus, contributing to the infection outcome to be either moderate, severe, or mild. The severity of COVID-19 infection in elderly patients, namely mortality, could be explained on the basis of a lower abundance of the host defensive miRNAs.

The upregulation of miRNA 197-5p is implicated in CV complications in SARS-CoV-2 patients (de Sanctis et al. 2020). SARS-CoV-2 miRNAs have been also found to inhibit ribosomal translation of some primary human proteins including olfactory receptor proteins (ORP), hemoglobin, and IFN, resulting in *dysosmia*, marked disruption of oxygen delivery to vital organs, and *generalized hypoxic* condition (Khan et al. 2020; Vavougios 2020). Additionally, several host miRNAs, namely miR-320a, miR-3188, miR-3661, miR-217, miR-429, and miR-421, may be involved in the deregulation of different pathways involved in the acute lung injury observed in SARS-CoV-2–infected patients (Islam and Khan 2020). Consequently, miRNAs can be the *key epigenetic modulator* behind the increased post-COVID-19 complications observed in some patients, but not others; therefore, they could be utilized for testing to predict COVID-19 infection severity (Guterres et al. 2020).

Khan et al. observed, by comparing the host miRNA profiles of 67 SARS-CoV-2 isolates from 24 different countries worldwide, several clusters and associated miRNAs. They correlated these clusters with the mortality rates across the globe (Khan et al. 2020), suggesting a link to higher susceptibility to SARS-CoV-2 infection observed in *the Europeans*.

Moreover, there is a possible link between host miRNAs and severity of the disease as well as treatment outcomes in some populations (Samaddar et al. 2020). For instance, host miRNAs in the *Indian population*, namely hsa-let-7a, hsa-miR101, hsa-miR125a-5p, hsa-miR126, hsa-miR222, hsa-miR23b, hsa-miR378, hsa-miR380-5, and hsa-miR98, can potentially target SARS-CoV-2 (Samaddar et al. 2020), where hsa-miR-27b is hypothesized to have a specific defensive role against SARS-CoV-2 in the Indian population (Sardar et al. 2020).

Another study analyzed miRNAs from five genomes of SARS-CoV-2 and identified 22 potential viral miRNAs being linked with 12 human miRNAs (Sarma et al. 2020), based on *nucleotide similarity and gene ontology*, where the interaction between human miRNAs and the viral genome may be involved in mediating the host pathway(s) which may/may not accelerate the virus pathogenic condition(s) (Gemmati et al. 2020).

Viral genome mutation and v-miRNA mutations

Mutation rate can greatly affect the SARS-CoV-2 host susceptibility, viral pathogenicity, and the antiviral immune response, which are, therefore, linked to disease severity and mortality rates (Abu-Izneid et al. 2020; Deng et al. 2020). These mutations can lead to either gain or loss of v-miRNA host-cell–binding sites, with subsequent changes in viral replication (Henzinger et al. 2020). For example, mutations in SARS-CoV-2 variant that bind to miR-4701-3p render the virus less prone to miRNA-mediated RNA decay, due to a reduced miR-4701-3p expression in the lung tissues (Mukherjee and Goswami 2020). The loss of miR-197-5p binding site, through viral mutations, results in viral transcript degradation, allowing SARS-CoV-2 to escape from the miRNA-mediated immune defense (Hosseini Rad and McLellan 2020). miRNA-based therapeutic options may serve as either miRNA antagonists and/or miRNA mimics (Henzinger et al. 2020; Abu-Izneid et al. 2020).

Long noncoding RNAs (lncRNAs)

Understanding the role of lncRNA (having a size of more than 200 nucleotides) in the deregulated cellular environment of SARS-CoV-2 infection is crucial, as it regulates processes involved during viral infection, viral proliferation, and cellular response (Turjya et al. 2020). Host lncRNA metastasis–associated lung adenocarcinoma transcript 1 (MALAT1) and

nuclear-enriched abundant transcript 1 (NEAT1) in infected SARS-CoV-2 cells could be used as potential biomarkers for monitoring infection progression and measuring disease severity (Henzinger et al. 2020; Vishnubalaji et al. 2020). Moreover, silencing of the MALAT1 lncRNA might lead to post-CoV-2 infection-CS reduction, where lncRNA acts like a sponge to prevent virally induced miRNAs to attach the host upregulated immune genes (Henzinger et al. 2020).

COVID-19-associated febrile temperatures were shown to induce widespread changes in the transcriptome that would affect the regulation of *multiple epigenetic pathway dysregulation as one of the hallmarks of CoV-2 infection*, one of which is lncRNA expression, that can lead to SARS-CoV-2 replication inhibition (Herder et al. 2020).

DNA methylation

The dynamic epigenetic modification, namely DNA methylation, could be useful for pointing out gene regulation, chromosome stability, and establishment of heterochromatin (Table 2) (Schäfer and Baric 2017; Menachery et al. 2018). Moreover, acquired DNA methylation changes may be a potential molecular biomarker in predicting adverse health outcomes (Franzen et al. 2020) and disease severity (Choudhary et al. 2020). DNA methylation signatures depend on the host cell type, gender, and age, which are risk factors associated with an increased risk of COVID-19 infection together with poor prognosis (Crimi et al. 2020) and with severe outcomes (Chlamydas et al. 2020; Franzen et al. 2020; Sang et al. 2020; Yao and Lawrence 2020).

Aging can affect *ACE2* gene DNA methylation levels and can mediate age-dependent differences in regard to host response (Franzen et al. 2020; Choudhary et al. 2020). One study indicated that age-associated hypomethylation at the CpG site located near the ACE2 transcription start site in the airway epithelial cells is correlated with an increased expression of *ACE2* gene (Franzen et al. 2020), allowing SARS-CoV-2 entry to the host cell.

Similarly, epigenetic modulation of TMPRSS2 involves enhanced methylation that reduces the S protein priming (Henzinger et al. 2020). Moreover, methylation of adenine within the mRNA molecule at position 6 (N6-methyladenosine, m6A) alters mRNA stability of both cellular and viral transcripts, affecting their translation efficiency and RNA-protein interaction (Choudhary et al. 2020).

Silent hypoxemia observed in some COVID-19 patients can lead to alteration of DNA methylation patterns (Beacon et al. 2020). Demethylation of IFN-regulated genes, $NF\text{-}_kB$ and the main cytokine genes, enhances the expression of more pro-inflammatory cytokines and chemokines, thereby increasing CS incidence, with an increased infection severity (El Baba and Herbein 2020). Epigenetic intervention affecting DNA methylation may be suggested as a primary and/or secondary preventive option.

Histone modifications

Posttranslational modifications in the histone protein as methylation, acetylation, and phosphorylation can occur leading to alterations in the DNA interactions with nuclear protein, which changes the chromatin architecture and gene activation (Ragia and Manolopoulos 2020). Previous investigations (Table 3) have shown that *ACE2* and *IL-6* genes are among a class of interferon-stimulated genes (ISGs) that can undergo epigenetic regulation through histone modifications and can be potential biomarkers for SARS-CoV-2 infection (Chlamydas et al. 2020; Sang et al. 2020). Pinto et al. have reported that the histone modification mono-methylation and trimethylation at the 4th lysine residue of the histone H3 protein (H3K4me1 and H3K4me3, respectively); acetylation of the lysine residue at N-terminal position 27 of the histone H3 protein (H3K27Ac) in the *ACE2* gene is associated with an increased ACE2 expression (Pinto et al. 2020). H3K9me2 is involved in DNA methylation and heterochromatin formation. H3K4me3 regulates TLRs which play an important role in the host's innate immune system (El Baba and Herbein 2020). Histone acetylation (H3K9Ac, H3K36Ac, and H4K5Ac) causes the suppression of the developed IL-8 and TNF-alpha levels in response to COVID-19 infection (El Baba and Herbein 2020). NAD-dependent histone deacetylase sirtuin 1 (silent mating type information regulation 2 homolog1) (SIRT1), which deacetylates transcription factors involved in cellular metabolism regulation, is associated with an increased ACE2 expression (Pinto et al. 2020) and is upregulated in COVID-19 patients' lungs with extreme chronic conditions (El Baba and Herbein 2020).

Acetylation and hypermethylation changes as *histone marks as another one of the hallmarks of CoV-2 infection* can lead to upregulation of the pro-inflammatory cytokines set (IL-1β, IL-6, IL-12, TNF-5-007) and chemokine (C-C motif) ligand (CCL2, 3, 5), CXCL8, CXCL9, and CXCL10 by the effector cells contributing to the fatal CS in severe COVID-19 cases (Ovsyannikova et al. 2020). Repressive histone marks high levels can result in an IL-12 and IL-1β level reduction, contributing to COVID-19 infection severity (Chlamydas et al. 2020).

SARS-CoV-2–infected patients are at higher risk of intravascular coagulation and thromboembolic events (Cattaneo et al. 2020). *Neutrophil extracellular trap* (NET) is a type of the innate immunity for pathogens entrapment, in which histone H3 modifications cause neutrophil cell death, platelet aggregation, and scaffold formation (Crimi et al. 2020). This later scaffold consists of DNA and histones, as well as chromatin fibers. NET scaffold may cause multiorgan damage and mortality in severely COVID-19–affected patients

(McCracken et al. 2020). Multiorgan damage is mediated via autoantibodies formation to severe NET formation (NETosis); a defense mechanism that neutrophils deploy as an alternative to phagocytosis, to constrain the spread of fungi, large bacteria, or viruses.

Wang et al. discovered that G9a, a histone methyltransferase that is overexpressed in COVID-19 patients, demonstrated high viral load and activates specific gene translation inducing an increased inflammatory reaction and T-cell function impairment or lymphopenia, which may contribute to the high mortality rate seen in those patients (Wang et al. 2020). Human identical sequence (HIS)–containing virus fragments can increase H3K27Ac enrichment in their genome corresponding regions and enable more expression of the inflammation-associated genes (Li et al. 2020).

Chromatin remodeling (Table 4)

Chromatin remodeling complex is composed of reversible histone and DNA modifications that controls chromatin composition and role (Schäfer and Baric 2017; Fadason et al. 2020). Euchromatin is more accessible, less tightly packed chromatin, that is linked with active marks like histone acetylation and H3 methylation at lysine 4. However, the repressed chromatin form, named heterochromatin, is linked with repressive marks like methylation of H3 at lysine 27 (H3K27me3) and lysine 9 (H3K9me2/3) (Beacon et al. 2020). Poor prognosis observed in elderly COVID-19 patients may be linked to the pre-existing reduction of ACE2 expression, controlled by chromatin structure and ACE2-related host-derived pathways imbalance (Fadason et al. 2020). Giroux et al. analyzed the response of peripheral blood mononuclear cell throughout SARS-CoV-2 infection of patients with different degrees of symptom severity. Giroux group demonstrated chromatin remodeling in certain innate immune populations (CD14+ monocytes) to be associated with divergence in symptom severity and the identified transcription factors, regulatory elements, and downstream pathways. All these would be potential prognostic markers for COVID-19 infection (Giroux et al. 2020).

ISG transcription initiation requires additional chromatin remodelers and transcription factors including ATP-dependent chromatin remodeling complex, in addition to inducing histone methylation and acetylation: H3K4me3 and H4Ac (Choudhary et al. 2020). It was found that SARS-CoV-2 can induce repression of *ACE2* via chromatin remodeling, therefore, altering the regulatory elements within ACE2 gene region that modulates the expression of genes *PIR* (encodes Pirin), *CA5BP1* (a pseudogene of CA5B), and *CA5B* (encodes mitochondrial carbonic anhydrase) in lung tissues. The gene products of these genes are involved in the NF_KB inflammatory responses and de novo pyrimidine synthesis, promoting an intracellular environment suitable for the viral replication (Fadason et al. 2020).

Summary

Molecular mechanisms of CoV-2 pathogenesis (Fig. 4) points to epigenetic(s); namely, the gene (DNA-methylation), its expression (noncoding RNA; microRNA; or lncRNA); or post-expression alteration = posttranslation (histone modifications; acetylation, de-acetylation, or methylation). Epigenetic modulations involve chromatin structure modulation or posttranscriptional modification by protein-RNA interaction or all together. Epigenetic landscape tends to contribute to variation in the host susceptibility to SARS-CoV-2 infection and to the host post-infection pathological features and severity of symptoms.

Study limitation

The context of the limitations lay in the limited availability of epigenetic routine markers and the inclusion of articles in English language only. Many observational studies were included due to the scarcity of RCTs, with the notion that observational studies cannot discover causality.

Conclusions

Epigenetics are molecular biomarkers that can regulate immunity-related gene targets through complex networks of virus-host cell interactions. Epigenetic pathways dysregulation is to be considered as *hallmarks of CoV-2 infection*. The current SRR has highlighted the crucial role of host and viral epigenetics during CoV-2 pandemic, necessitating the importance of implementing "epigenetic diagnostics" and/or "epigenome nation-wide research." The human epigenetic(s) alteration(s) observed in coronavirus-infected patients are listed and were found to be linked to COVID-19 susceptibility, severity of infection, and/or outcome.

Prospective

(1) Epigenetic tests for SARS-CoV-2 are warranted to categorize patients into various treatment classes as an essential step for national PM practice. (2) The urge to develop or repurpose epi-drugs to various epigenetic target(s) is the current priority of drug design research in order to control this multi-wave rapidly and constantly mutating pandemic.

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Abbreviations ACE2, angiotensin-converting enzyme 2; ADAM17, a disintegrin and metalloproteinase domain 17; CA5B, carbonic anhydrase 5b; CCL, chemokine (C-C motif) ligand; CCR4-Not, CNot4, carbon catabolite repression—negative on TATA-less subunit 4; CS, cytokine storm; CV, cardiovascular; CXCL16, C-X-C motif chemokine ligand 16; ErbB, erythroblastic leukemia viral oncogene type I receptor family epidermal growth factor (EGF) receptor (EGFR); FAK, focal adhesion kinase; FGF, fibroblast growth factor; hsa, human microRNA; HCoV-OC43, human coronavirus OC43; H3K4me1, mono-methylation at the 4th lysine residue of the histone H3 protein; H3K4me3, trimethylation at the 4th lysine residue of the histone H3 protein; H3K27Ac, acetylation of the lysine residue at N-terminal position 27 of the histone H3 protein; HIS, human identical sequences; IFN, interferons; IGF-1, insulin-like growth factor-1; IL-, interleukin-; ISGs, interferon-stimulated genes; JAK, Janus kinase; JARID1B, Jumonji/ARID domain-containing protein 1B; LncRNA, long noncoding RNAs; MALAT1, metastasis-associated lung adenocarcinoma transcript1; MAPK, mitogen-activated protein kinases; miRNAs, microRNAs; mRNAs, messenger RNAs; mTOR, mechanistic target of rapamycin; NEAT1, nuclear-enriched abundant transcript 1; NET, neutrophil extracellular traps; NETosis, NET formation; ncRNAs, nonprotein-coding RNAs; NF_KB, nuclear factor kappa B; ORP, olfactory receptor proteins; PAR, protease-activated receptor; PDGF, platelet-derived growth factor; PM, precision medicine; PRISMA, preferred reporting items of the systematic review and meta-analysis; p53, phosphoprotein 53; RCT, randomized controlled clinical trial; S, spike; SARS, sever acute respiratory syndrome; SDGs, sustainable development goals; SOCS, suppressor of cytokine signaling; S1P1, sphingosine-1-phosphate receptor1; SIRT1, NAD-dependent histone deacetylase sirtuin 1; Sirtuin1, silent mating type information regulation 2 homolog 1; SRR, systematic rapid review; STAT5B, signal transducer and activator of transcription 5B; TGF-β1, transforming growth factor-beta 1; TLRs, toll-like receptors;; TMPRSS 2, transmembrane protease serine 2; TNF-alpha, tumor necrosis factor-alpha; TRAF6, tumor necrosis factor receptor-associated factor 6; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; 3′UTR, 3′ un-translated region; VEGF, vascular endothelial growth factor; Wnt, wingless-related integration site; v-miRNAs, viral-miRNAs

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Author contribution SGA, the senior investigator, setting the idea, resolving investigator authors' disagreements, revising Table 1 and PRISMA flowchart, revising the written first manuscript draft, and rewriting and revising till the final draft. AAR, AMB, LAE1, NS, LAE2, NA, and MMM: selection of studies, titles, and abstracts for eligibility; identification of studies meeting the inclusion criteria; rechecking selected studies, figures, and GA drafting; PRISMA flowchart drafting; Table 1 synthesis; writing of the first manuscript draft and rewriting till the final form. NMH, the chief investigator: setting the idea, registering to PROSPERO, resolving investigator authors' disagreements, setting figures and GA drafting, revising figures and PRISMA flowchart drawing, setting and revising Table 1 synthesis, revising the first manuscript draft, and rewriting and revising the final manuscript till submission.

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Declarations

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