Review Article:

Involvement of Epigenetics in the Pathogenesis, Testing and Management of Coronavirus Disease 2019 (COVID-19) Pandemic: A Narrative Review

Tajudeen Yahaya[1*], Esther Oladele[2], Aminu Muhammed[1], Abdulhakeem Haruna[1], Usman Liman[3]

1. Department of Biological Sciences, Federal University Birnin-Kebbi, Birnin-Kebbi, Nigeria.
2. Biology Unit, Distance Learning Institute, University of Lagos, Lagos, Nigeria.
3. Department of Biochemistry and Molecular Biology, Federal University Birnin-Kebbi, Nigeria.

*** Corresponding Author:**
Tajudeen Yahaya, PhD.
Address: Department of Biology, Federal University Birnin-Kebbi, Birnin-Kebbi, Nigeria.
Phone: +234 (80) 98233774
E-mail: yahayatajudeen@gmail.com

Article info:
Received: 21 Nov 2020
Accepted: 27 Feb 2021

Keywords:
Coronavirus, Epigenome, Interferons, MicroRNAs, SARS-CoV-2

ABSTRACT

Background: There is an intense search for the Coronavirus Disease 19 (COVID-19) cure, to stem the spread and burden of the disease worldwide. Studies revealed that epigenetic modifications impact the pathogenesis of some COVID-19 cases, which can be used as therapeutic targets.

Objectives: This review articulated the role of epigenetics in the pathogenesis and management of COVID-19.

Methods: Relevant articles published between January 2000 and November 2020 were retrieved from reputable academic databases, including PubMed, SpringerLink, Scopus, and Google Scholar.

Results: Epigenetic modifications in the COVID-19's pathogen, called the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and host's cells may influence susceptibility or resistance to the disease. Notably, abnormal Deoxyribonucleic Acid (DNA) methylation and histone modification involving immune regulatory genes and molecules, such as cytokines and interferon-regulated genes may compromise immune function and enhance the host's susceptibility and disease severity. The hypomethylation of SARS-CoV-2's receptor, called the Angiotensin-Converting Enzyme 2 (*ACE2*), causing its overexpression, can also enhance SARS-CoV-2's infectivity. Moreover, SARS-CoV-2 can hijack the host's MicroRNA (miRNA) using its miRNA and compromise the immune function, increasing its infectivity. Fortunately, epigenetic changes are reversible; thus, a therapy that targets the epigenetic changes in the affected case may reverse COVID-19.

Conclusion: Modifications in the SARS-CoV-2 or host epigenome promote the pathogenesis and severity of COVID-19. Epigenetic changes are reversible, so healthcare providers are advised to formulate therapeutic procedures that target the causal mechanisms in the affected individual.

Citation Yahaya T, Oladele E, Muhammed A, Haruna A, Liman U. Involvement of Epigenetics in the Pathogenesis, Testing and Management of Coronavirus Disease 2019 (COVID-19) Pandemic: A Narrative Review Pharmaceutical and Biomedical Research. 2021; 7(3):161-170. http://dx.doi.org/10.18502/pbr.v7i3.7697

http://dx.doi.org/10.18502/pbr.v7i3.7697

Introduction

Coronavirus Disease 2019 (COVID-19) broke out in December 2019 and shortly spread across several countries, leading to high mortality worldwide [1]. The causative agent of COVID-19 is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the genus *Betacoronavirus* [2]. The virus is related to SARS-CoV and the Middle East Respiratory Syndrome (MERS-CoV) [3]. However, SARS-CoV-2 has a lower mortality rate (2.3%), compared to SARS-CoV (9.5%) and considerably lower than that of MERS-CoV (34.4%) [2]. The relatively low severity of SARS-CoV-2 may explain its easy and rapid spread among individuals, compared to MERS-CoV and SARS-CoV [2]. The symptoms of COVID-19 are mainly related to the respiratory system; most patients may return to normal without requiring special treatment [1]. Older people and those with underlying medical problems, such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more prone to develop serious COVID-19 [1]. There is also increasing evidence that numerous COVID-19 patients may remain asymptomatic [4].

COVID-19 pandemic caused a global lockdown of activities, which affected national budgets and businesses, and nearly caused an economic meltdown in some countries. These conditions have led to an intense search for the relevant vaccines and drugs, to reduce the spread of the virus and cure the infected. Some studies suggested that epigenetic modifications in individuals and SARS-CoV-2 genomes contribute to the virus's pathogenesis. Epigenetic modifications are heritable changes in gene expression and function without altering the genetic makeup [5]. Epigenetic changes may alter the expression of genes involved in immune response as well as the viral genome, predisposing to or protecting from infection [6]. Thus, understanding the mechanisms by which SARS-CoV-2 epigenetically hijacks the cellular apparatus may help develop vaccines and therapeutic procedures. Accordingly, this review articulated epigenetic mechanisms in the host and viral genomes involved in the pathogenesis of COVID-19, as well as potential epigenetic drugs.

Materials and Methods

Database searching and search strategy

Academic databases searched for relevant information included PubMed, SpringerLink, Scopus, Google Scholar, and Semantic Scholar. Selected search terms used to retrieve articles consisted of "epigenetics, epigenetic mechanisms, coronavirus diseases, coronavirus disease 2019, pathology of COVID-19, SARS-CoV-2, epigenetic testing, and viral infections". Other applied search terms included "the role of DNA methylation in COVID-19, the role of histone modification in COVID-19, the role of non-coding RNAs in COVID-19, and epigenetic drugs". The articles collected from each database were pooled together and duplicates were removed using EndNote.

Criteria for the inclusion and exclusion of articles

Included articles were in English with a focus on the epigenetic aspects of COVID-19. Furthermore, only articles published from January 2000 to November 2020 were included. Excluded articles consisted of those without available full texts and those that failed to meet the above-mentioned inclusion criteria.

Seventy-Five articles were retrieved from the searched databases (Figure 1). However, after removing duplicates, 68 articles were retained. The 68 articles were subjected to an eligibility test and 60 articles scaled through. Of the 60 articles, 53 focused on the study aim; thus, made the final selection.

Mechanistic links between epigenetics and COVID-19

Epigenetics is described as the study of genetic and non-genetic factors that control phenotypic variations [7]. Epigenetic modifications turn genes on or off; thus, altering the expression or function of the genes without altering the genetic constitutions [7, 8]. Epigenetic processes are necessary for healthy cellular activities, such as growth and development. However, changes in genes that ideally protect against certain diseases could make individuals more susceptible to diseases [8]. Characteristics that can induce epigenetic changes include certain diets and environmental chemicals [8]. Microorganisms, such as hepatitis B and Epstein-Barr Virus (EBV), as well as intracellular bacteria, can also epigenetically manipulate the host cells to enhance their maintenance, replication, and transmission [9]. Coronaviruses are suspected to alter the human epigenome, allowing them to bypass the host's immune system and successfully mount and spread infection [6, 7]. Three major epigenetic mechanisms through which microorganisms, including coronaviruses, can manipulate the host epigenome to establish an infection are Deoxyribonucleic Acid (DNA) methylation, histone modifications, and non-coding RNA-associated gene silencing [10]. Articles that focused on the

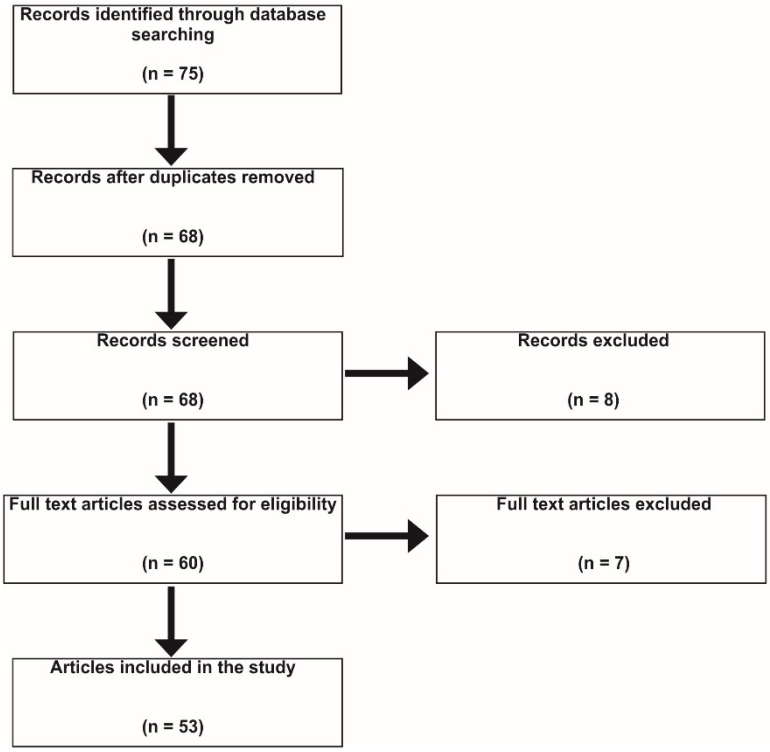

Figure 1. The PRISMA flow diagram of article selection

mechanistic links between epigenetics and COVID-19 are summarized in Table 1.

The role of DNA methylation in COVID-19 pathogenesis

DNA methylation is an epigenetic mechanism involving the addition of a methyl group to a cytosine residue in a Cytosine-guanine Sequence (CpG) [10]. There exist clusters of CpG sites in the cells (i.e., CpG island) whose methylation in a gene promoter may silence the gene [10]. The binding of methyl groups is modulated by a group of enzymes collectively called DNA Methyltransferases (DNMTs), which include DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L [5, 10]. DNA methylation is involved in microbial infection, of which, the abnormal methylation of certain genes involved in infection mounting and immune response may enhance viral infection. Some microbes may also epigenetically manipulate the host cell to enhance infectivity. SARS-CoV-2, in particular, invades the host cells by attaching to a receptor encodes by a gene, called Angiotensin-Converting Enzyme 2 (*ACE2*). However, the binding affinity of the virus depends on the methylation and expression of *ACE2*, i.e., influenced by the functional state of the immune system.

The immune function is influenced by age, health status, gender, and even the genome of SARS-CoV-2. The differential methylation and expression of *ACE2* in individuals may therefore be partly responsible for the variations observed in COVID-19 vulnerability. Hypomethylation increases the expression and virus binding ability of the *ACE2*, while hypermethylation decreases it. Diseases (health status), particularly immune-mediated diseases, can cause hypomethylation of the *ACE2*, resulting in its overexpression and increased affinity for SARS-CoV-2.

Table 1. Mechanistic links between epigenetics and COVID-19

Mechanisms	References
DNA methylation	5, 10, 11, 12, 13, 14, 15, 16, 17, 18
Histone post translational modification	5, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26
Non-Coding RNA* gene silencing	10, 27, 28, 29, 30, 31, 32, 33

* RNA: Ribonucleic Acid

The hypomethylation of *ACE2* in diseased individuals may be further aggravated by a viral infection. For example, Sawalha et al. [11] indicated that oxidative stress caused by SARS-CoV-2 exacerbated the hypomethylation of *ACE2*-induced lupus, increasing the odds of infection.

Females are prone to encounter the effects of disease-mediated hypomethylation of *ACE2*. This is because the reduced DNA methylation may cause a defective X chromosome inactivation [12]. This may further upregulate X-linked genes, which include the *ACE2*. DNA methylation is essential for inactivating the X chromosome in which expressing one copy of the X chromosome in females is repressed [11]. This is necessary to maintain the normal expression level of female cells, comparable to male cells [11]. In a study of COVID-19 patients by Corley and Ndhlovu [13], DNA methylation analysis at two CpG sites related to the *ACE2* gene suggested that female subjects were significantly hypomethylated, compared to males [13]. This could have resulted from the disruption of inactivation of the X chromosome, upregulating its genes, including the gene that codes for *ACE2*; thus, culminating in increased susceptibility to COVID-19.

Aside from *ACE2*, immune-related diseases, like lupus may cause the demethylation of interferon-regulated genes, like the nuclear factor kappa light chain enhancer of activated B cells (NFκB), as well as certain cytokine genes [11]. The demethylation of these genes may cause an overreaction of the immune response to SARS-CoV-2, resulting in cytokine storm [11]. A cytokine storm may induce autoimmunity, leading to cell death and organ failure [14]. Multiple other immune-mediated diseases may produce similar effects as lupus. For example, Chai et al. [15] observed the hypomethylation and overexpression of *ACE2* in COVID-19 patients expressing different tumor types. Other members of the coronavirus family, such as MERS-CoV and SARS-CoV, as well as H5N1 influenza, have been manifested to compromise the immune function through DNA methylation and histone modifications to mount infections [16]. Additionally, SARS-CoV uses *ACE2* as the receptor and can epigenetically induce overexpression of the receptor to cause infection [17]. Collectively, these data revealed that epigenetic modifications may promote viral entry, infectivity, abnormal immune reactions to SARS-CoV-2, and severe COVID-19 [11, 14].

Regarding aging, it may cause the hypomethylation of *ACE2* through immune function decline, compromising viral defenses, including adaptive immune memory [18]. The methylation of the CpGs in the *ACE2* promoter declines with age [18], which could overexpress the *ACE2* gene and increase its viral binding affinity. In a genome-wide DNA methylation study of freshly isolated airway epithelial cells of non-asthmatics SARS-CoV-2 patients, the levels of methylation of a CpG site (cg08559914) near the *ACE2* gene correlated with biological age [13]. Furthermore, RNA sequences from the lung of young males presented significantly low methylation and high levels of transcription, compared with fetal and female lungs [13]. Thus, the decreasing methylation of *ACE2* as aging progress could partly explain while most elderly manifest a more severe form of COVID-19 [13]. Coronaviruses may facilitate the aging of the immune system through epigenetic alterations, enhancing the virus's infectivity [18]. MERS-CoV, for instance, may compromise host antigen presentation by disrupting DNA methylation, silencing genes that encode major histocompatibility complexes [18].

The role of histone modifications in COVID-19 pathogenesis

Histones are the major proteins (called chromatin) in the chromosome that condense and help package DNA in the chromosomes [19]; thus, histone modifications may affect numerous biological processes. Histone modifications are changes in the chromatin structure that may alter the expression and function of the embedded genes [20]. The histone's N-termini, called histone tails, extend from the globular protein unit, making the tails the targets for histone modifications [21]. Mechanisms that can modify histones include acetylation, methylation, phosphorylation, and ubiquitylation [5]. However, acetylation and methylation are the most frequent histone modifications [5]. The enzymes that catalyze histone acetylation and methylation are Histone Acetyltransferases (HATs) and Histone Methyltransferases (HMTs), while Histone Deacetylases (HDACs) and Histone Demethylases (HDMs) catalyze deacetylation and demethylation, respectively [20]. In humans, factors that can modify histones include diets, chemicals, pathogens, as well as diseases, and aging [16]. Certain diseases may modify the histone, upregulating the *ACE2* and increasing COVID-19 susceptibility. In a study that compared lung transcriptomes in individuals with comorbidities related to severe COVID-19, such as diabetes mellitus and vascular diseases, *ACE2* was overexpressed in the individuals, compared to the non-affected individuals [22]. Notably, the analyses revealed histone modification, which upregulated *ACE2*-related genes, such as Histone Acetyltransferase 1 (HAT1), Histone Deacetylase 2 (HDAC2), and Lysine Demethylase 5B (KDM5B) [22]. This finding suggested that individuals with such diseases may experience a high odds of expressing severe COVID-19.

There is a dearth of literature on the histone-modifying activities of SARS-CoV-2. However, some studies documented highly pathogenic viruses, including the coronaviruses may induce the loss of the antiviral functions of interferon-regulated genes within the host by repressing the histone, enhancing infection. A study compared the interferon-regulated gene response patterns following Asian avian influenza (H5N1 & HPAI), SARS-CoV, and MERS-CoV infections.

The relevant data suggested that the viruses used similar approaches to antagonize the global interferon-regulated gene response [23]. The viruses induce repressive histone modifications, which downregulate interferon-regulated genes' expression [23]. Another study analyzed the epigenetic changes following influenza infection; accordingly, the hypoacetylation of the histone was observed [24]. The epigenetic changes inactivate embedded genes, enhancing influenza virus infection [24]. Particularly, the influenza virus induces the hypomethylation of histone H3 lysine 79 (H3K79), which increases the virus' replication. In the same study, the methylation of H3K79 was demonstrated to control the replication of the influenza virus and some other potent interferon-disrupting viruses [24]. Thus, H3K79 methylation may help control interferon disruption by viral pathogens [24]. Furthermore, SARS-CoV was suggested in a study to change histone methylation, accompanied by the overreaction of interferon-response genes [18]. SARS-CoV-2, being genetically similar to SARS-CoV, may likely induce a similar immune response.

Aging may accelerate histone modification, declining immune function, and promoting infectivity. Changes in chromatin are increasingly linked with cellular and organismal aging in several species [25]. Immune cells from young individuals possess a strong and healthy chromatin structure protected from damage by long telomeres and compacted heterochromatin [25]. Furthermore, chromatin in aged cells, expresses shortened telomeres, disrupted epigenome, and loose heterochromatin [25].

Data on age-related genome-wide changes in histone modifications in mammalian cells are scarce. However, the RNA sequence of the mouse germ cell line manifested histone modification, which reduced histone H3 lysine 27 trimethylation (H3K27me3) and upregulated *ACE2* expression. A similar observation was documented in human embryonic stem cells in which *ACE2* was overexpressed in the absence of the enhancer of zeste homolog 2 (EZH2), the major enzyme catalyzing H3K27me3 [26].

The role of Non-coding RNAs in COVID-19 pathogenesis

Non-Coding RNAs (ncRNAs) are functional RNA molecules, i.e., transcribed from DNA but not translated into proteins [10]. Non-Coding RNAs include miRNA, Small Interfering RNA (siRNA), Piwi Interacting RNA (piRNA), and Long Non-Coding RNA (lncRNA) [10]. Non-coding RNAs control gene expressions at transcriptional and post-transcriptional stages [10]. However, not all ncRNAs are involved in epigenetic modifications [10]. Those that affect epigenetic modifications can be classified into the short ncRNAs (<30 nucleotides) and the long ncRNAs (>200 nucleotides) [10]. The short ncRNAs can be divided into 3 subgroups of miRNAs, siRNAs, and piRNAs.

RNA post-transcriptional modifications by ncRNAs play critical roles in the life cycles of certain viruses, including human coronavirus [27]. Adenosine methylation in particular, such as N6-Methyladenosine (m6A), N6-adenosine methylase (m6Am), and 2'-O-methylation (2′-O-me) were reported to affect the viability of specific RNA viruses such as coronaviruses [27]. Adenosine methylation modulates viral cap structures, viral replication, innate sensing pathways, and the innate immune response [27]. Moreover, coronaviruses and other virus species encode their methyltransferase for self-methylating adenosine residues, promoting immune evasion [27]. This makes the viral epitranscriptome an attractive target for therapeutic intervention [27]. N6-Methyladenosine is the most common and abundant eukaryotic RNA modification, accounting for >80% of all RNA methylations [27]. N6-Methyladenosine exhibits pro- and anti-viral activities, depending on the virus species and host cell type [27]. The RNA genome of SARS-CoV-2 contains >50 potential m6A sites and ≥0.64% of all adenosines, or 0.18% of all bases, in SARS-CoV-2 RNA could be m6A [27]. The gain or loss of m6A can cause significant functional changes to RNA viruses, altering host cell fusion/entry, replication, transmission, pathogen intensity, and immune evasion [27]. The m6A epitranscriptome of host cells influences host resistance and can undergo alterations after viral infection [27]. Accordingly, epigenetic drugs and therapies that target viral and host m6A modifications may control RNA viral infection, including COVID-19, in patients expressing epigenetic changes [27].

Several studies revealed that the miRNAs of the host may attach to the genomes of the RNA virus to prevent the translation and replication of the virus [28]. Sometimes, the host may induce changes in miRNA expression, increasing its antiviral effects or activities; thus,

decreasing viral replication [28]. However, some RNA viruses can change the expression of the host miRNAs, repressing the host transcriptome, culminating in increased viral infectivity [28]. For instance, the influenza virus was introduced to repress host miR-24, increasing furin protease levels as well as the virus's replication [29]. Furthermore, miR-146a-5p overexpression following a coronavirus infection of human hepatocytes enhanced the virus's replication and infectivity [30]. In a study that sequenced lung samples from SARS-CoV and influenza virus-infected mice by Peng et al. [32], the differential expression of several small ncRNAs, including miRNAs (small nucleolar RNAs) were observed. Collectively, viruses encode miRNAs that control the expression of both human and viral genes, contributing to the pathogenicity of viruses [32].

In a genome scanning of SARS-CoV-2, viral and human miRNAs, as well as targets and biological processes involved in the pathogenesis of the virus, were established. Host immune response and epigenomes are the main cellular processes regulated by the miRNAs of SARS-CoV-2 [33]. It was observed that human miR-4661-3p targets the S gene of SARS-CoV-2 to control it. However, SARS-CoV-2 miRNA MR147-3p enhances the expression of transmembrane serine protease 2 (TMPRSS2) genes, increasing SARS-CoV-2 infection. As a result, the virus genome can hijack host miRNA to compromise host biological processes involved in immune response [33]. A virus can suppress the RNA-interference pathway of the host by using viral miRNA or proteins to target cellular or viral transcripts [32].

Epigenetic tests for COVID-19

There exist epigenetic tests that can accurately detect epigenetic modifications caused by SARS-CoV-2. According to Karow [34], and epigenetic test that detects epigenetic changes in DNA from blood samples was developed by researchers from some medical institutions, notably Mount Sinai's Icahn School of Medicine. The test detects disease-specific DNA methylation changes, which can be used to detect SARS-CoV-2 early. Interestingly, the new epigenetic test gives an appropriate COVID-19 diagnosis where genetic tests, such as exome sequencing and microarrays are ineffective [34]. Researchers and clinicians can also use the methylation profiling provided by the epigenetic test to distinguish severe cases from mild ones [34].

Some applications have also been developed which can help clinicians efficiently detect SARS-CoV-2, determine the risks and severity of COVID-19, and can be used to personalize treatment for patients. For instance, a company known as Diagenode offers tools, such as Megaruptor 3 and MicroPlex Library Preparation for sample preparation to sequence IGH/MHC immunology gene regions [35]. The company also produces RRBS/WGBS/MeDIP kits and histone modification antibodies and ChIP kits for global methylation and histones/chromatin modifications detection, respectively [35]. Generally, these tools can help detect DNA methylation alterations induced by SARS-CoV-2, i.e., effective to conduct large human cohort studies [35]. The tools can also characterize genomic regions that are involved in the immune response to SARS-CoV-2, to determine the severity of the disease. Furthermore, the tools can characterize the viral genome, to understand viral mutations [35].

Potential epigenetic drugs for COVID-19

There is no specific epigenetic drug or preparation for COVID-19. However, epigenetic mechanisms are similar in all cellular activities and disease pathologies; therefore, some epigenetic drugs formulated for other diseases may be effective in managing COVID-19. COVID-19 induced by the overexpression of *ACE2* due to DNA hypomethylation can be reversed or reduced by methyl-adding epigenetic drugs. Methyl donating compounds, such as folate may reverse hypomethylation in COVID-19 patients and normalize the expressions of *ACE2* [36]. Folate is a water-soluble B vitamin, i.e.,

Table 2. The potential epigenetic drugs for COVID-19

Epigenetic Drugs	References
Methyl-adding epigenetic drugs	36, 37, 38, 39, 40
I-BET151	5, 41, 42
Oligonucleotides (anti-miRNAs)	43, 44, 45, 46, 47
Histone inhibitors	48, 49, 50, 51, 52, 53

known to boost DNA methylation and epigenetic configuration [37]. Other compounds that contain a methyl group include methionine, choline, betaine, and vitamin B-12 [38, 39]. Alternatively, hypomethylation can be reversed by blocking the enzyme that catalyzes it, called Ten-Eleven Translocation (TET) [40].

In cases where the virus compromises the immune function and upregulates the immune cells, like cytokines, causing an inflammatory response and cytokine storms, some epigenetic drugs may neutralize or repress the immune cells. Some epigenetic drugs have been developed along this line, notable among which is an epigenetic drug known as I-BET151 [5]. The drug was developed by researchers at Harvard Medical School and GlaxoSmithKline and was demonstrated to repress overreactive cytokines, macrophages, T cells, among several immune cells [41, 42]. The drug does these by deactivating NFkB-mediated genes. I-BET151 also boosts the expression of some anti-inflammatory molecules [42].

For COVID-19 induced by the overexpression of viral miRNAs due to hypermethylation, complementary single-stranded oligonucleotides otherwise called anti-miRNAs can be used to suppress the virus's infectivity [43]. The hypomethylation of the host miRNAs makes it to be susceptible to SARS-CoV-2; it can also be normalized by adding RNA molecules analogous to the precursors of the target miRNA or adding oligonucleotides that mimic the mature form of the miRNA of interest [44]. Some proven anti-miRNAs include Locked Nucleic Acid (LNA), antagomirs, morpholinos, byetta, victoza, trulicity, janu-via, onglyza, and tradjenta [45-47].

Histone post-translational modification is performed by some enzymes, such as Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs). Thus, for COVID-19 that initiates with histone modification, blocking, or deleting these enzymes may be helpful [48, 49]. Some common histone inhibitors which have been tested on some diseases, such as cancers and diabetes are RGFP966, vorinostat, romidepsin, and belinostat [50, 51]. Several dietary substances are under investigation as potential HDAC and HAT inhibitors. In particular, sulforaphane (an isothiocyanate isolated from broccoli sprouts) and diallyl disul-fide (an organosulfur compound in garlic), was demonstrated to act as HDAC inhibitors [52, 53]. Table 2 presents a brief recap of potential epigenetic drugs for COVID-19.

Conclusion

The current review study established that epigenetic modifications in the human and SARS-CoV-2 genome impact COVID-19 pathogenesis. Alterations in epigenetic mechanisms, such as DNA methylation, histone modification, and non-coding RNAs may compromise the immune system and enhance host susceptibility to COVID-19. The alterations may also overexpress the virus's receptor, known as *ACE2*, increasing the virus' binding affinity and infectivity. These alterations may be induced by the virus's genome or the host's cellular processes, such as aging and certain diseases. Thus, the elderly and diseased are more susceptible and often expressed a more severe form of COVID-19. Epigenetic mechanisms are reversible and, as such, a therapeutic strategy that targets the epigenetic mechanisms that modulated COVID-19 in the affected individuals may reverse the disease.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and Supervision: Tajudeen Yahaya; Methodology: Tajudeen Yahaya and Esther Oladele; Investigation, writing, Original draft, review and editing: All authors; Data Collection: Aminu Mohammed, Abdulhakeem Haruna, and Usman Liman; Data Analysis: Aminu Mohammed, Abdulhakeem Haruna, and Usman Liman.

Conflict of interest

The authors declared no conflict of interest.

References

[1] World Health Organization (WHO). Coronavirus disease (COVID-19) [Internet]. 2020 [Updated 2021 September 22]. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1.

[2] Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5(4):536-44. [DOI:10.1038/s41564-020-0695-z.] [PMID] [PMCID]

[3] Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: Are they closely related? Clin Microbiol Infec. 2020; 26(6):729-34. [DOI:10.1016/j.cmi.2020.03.026.] [PMID] [PMCID]

[4] Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2021; 54(1):12-6. [DOI:10.1016/j.jmii.2020.05.001] [PMID] [PMCID]

[5] Yahaya T, Oladele E, Shemishere U, Abdulrau'f M. Role of epigenetics in the pathogenesis and management of type 2 diabetes mellitus. Translation. 2019; 6(6):20-8. [DOI:10.46570/utjms.vol6-2019-319]

[6] Abidi M. Understanding COVID-19 through the lens of epigenetics [Internet]. 2020 [Updated 2020 April 15]. Available from: https://www.jhunewsletter.com/article/2020/04/understanding-covid-19-through-the-lens-of-epigenetics

[7] Crowley N. A look in to the epigenetics of a Coronavirus infection [Internet]. 2020 [Updated 2020 March 10]. Available from: https://www.whatisepigenetics.com/a-look-into-the-epigenetics-of-a-coronavirus-infection/

[8] National Institute of Health. Epigenomics and epigenetics research [Internet]. 2020 [Updated 2020 June 23] . Available from: https://epi.grants.cancer.gov/epigen/

[9] Fischer N. Infection-induced epigenetic changes and their impact on the pathogenesis of diseases. Semin Immunopathol. 2020; 42(2):127-30. [DOI:10.1007/s00281-020-00793-1] [PMID] [PMCID]

[10] Al Aboud NM, Tupper C, Jialal I. Genetics, epigenetic mechanism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. [PMID]

[11] Sawalha AH, Zhao M, Coit P, Lu Q. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immunol. 2020; 215:108410. [DOI:10.1016/j.clim.2020.108410] [PMID] [PMCID]

[12] Lu Q, Wu A, Tesmer L, Ray D, Yousif N, Richardson B. Demethylation of CD40LG on the inactive X in T cells from women with lupus. J Immunol. 2007; 179(9):6352-8. [DOI:10.4049/jimmunol.179.9.6352] [PMID]

[13] Corley MJ, Ndhlovu LC. DNA methylation analysis of the COVID-19 host cell receptor, Angiotensin I Converting Enzyme 2 gene (ACE2) in the respiratory system reveal age and gender differences. Preprints 2020; 2020030295. https://www.preprints.org/manuscript/202003.0295/v1

[14] Szakal FD. Epigenetics could explain why COVID-19 affects people differently [Internet]. 2020 [Updated 2021 September 22]. Available from: https://www.whatisepigenetics.com/epigenetics-could-explain-why-covid-19-affects-people-differently/

[15] Chai P, Yu J, Ge S, Jia R, Fan X. Genetic alteration, RNA expression, and DNA methylation profiling of Coronavirus disease 2019 (COVID-19) receptor ACE2 in malignancies: A pan-cancer analysis. J Hematol Oncol. 2020; 13(1):43. [DOI:10.1186/s13045-020-00883-5.] [PMID] [PMCID]

[16] Menachery VD, Eisfeld AJ, Schäfer A, Josset L, Sims AC, Proll S, et al. Pathogenic influenza viruses and coronavirusesutilize similar and contrasting approaches to control interferon-stimulated gene responses. mBio. 2014; 5(3):e01174-14. [DOI:10.1128/mBio.01174-14] [PMID]

[17] Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020; 63(3):457-60. [DOI:10.1007/s11427-020-1637-5] [PMID] [PMCID]

[18] Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY). 2020; 12(10):9959-81. [DOI:10.18632/aging.103344.] [PMID] [PMCID]

[19] Cheriyedath S. Histone Modification [Internet]. 2020 [Updated 2021 September 22]. Available from: https://www.news-medical.net/life-sciences/Histone-Modification.aspx

[20] Tajudeen YO, Shemishere UB. Role of epigenetics and therapies for Type 1 Diabetes Mellitus: A narrative review. J Health Soc Sci. 2019; 4(2):199-212. https://journalhss.com/wp-content/uploads/jhss42_199-212.pdf

[21] Schäfer A, Baric RS. Epigenetic landscape during Coronavirus infection. Pathogens. 2017; 6(1):8. [DOI:10.3390/pathogens6010008] [PMID] [PMCID]

[22] Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet. 2007; 8(4):253-62. [DOI:10.1038/nrg2045] [PMID] [PMCID]

[23] Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ogava RLT, et al. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. J Infect Dis. 2020; 222(4):556-63. [DOI:10.1093/infdis/jiaa332.] [PMID] [PMCID]

[24] Marcos-Villar L, Díaz-Colunga J, Sandoval J, Zamarreño N, Landeras-Bueno S, Esteller M, et al. Epigenetic control of influenza virus: Role of H3K79 methylation in interferon-induced antiviral response. Sci Rep. 2018; 8(1):1230. [DOI:10.1038/s41598-018-19370-6.] [PMID] [PMCID]

[25] Keenan CR, Allan RS. Epigenomic drivers of immune dysfunction in aging. Aging Cell. 2019; 18(1):e12878. [DOI:10.1111/acel.12878] [PMID]

[26] Li Y, Li H, Zhou L. EZH2-mediated H3K27me3 inhibits ACE2 expression. Biochem Biophys Res Commun. 2020; 526(4):947-52. [DOI:10.1016/j.bbrc.2020.04.010] [PMID] [PMCID]

[27] Epigentek. The potential for m6A RNA methylation research of SARS-CoV-2 (2019 Novel Coronavirus) [Internet]. 2020 [Updated 2021 September 22]. Available from: https://www.epigentek.com/catalog/supporting-rna-research-of-coronaviruses-lp-29.html

[28] Trobaugh DW, Klimstra WB. MicroRNA regulation of RNA virus replication and pathogenesis. Trends Mol Med. 2017; 23(1):80-93. [DOI:10.1016/j.molmed.2016.11.003] [PMID] [PMCID]

[29] Loveday EK, Diederich S, Pasick J, Jean F. Human microRNA-24 modulates highly pathogenic avian-origin H5N1 influenza A virus infection in A549 cells by targeting secretory

pathway furin. J Gen Virol. 2015; 96(Pt 1):30-9. [DOI:10.1099/vir.0.068585-0.] [PMID]

[30] Bandiera S, Pernot S, El Saghire H, Durand SC, Thumann C, Crouchet E, et al. Hepatitis C virus-induced upregulation of microRNA miR-146a-5p in hepatocytes promotes viral infection and deregulates metabolic pathways associated with liver disease pathogenesis. J Virol. 2016; 90(14):6387-400. [DOI:10.1128/JVI.00619-16] [PMID] [PMCID]

[31] Peng X, Gralinski L, Ferris MT, Frieman MB, Thomas MJ, Proll S, et al. Integrative deep sequencing of the mouse lung transcriptome reveals differential expression of diverse classes of small RNAs in response to respiratory virus infection. mBio 2011; 2(6):e00198-11. [DOI:10.1128/mBio.00198-11] [PMID]

[32] Moen U. Silencing viral microRNA as a novel antiviral therapy? J Biomed Biotechnol. 2009; 2009:419539. [DOI:10.1155/2009/419539.] [PMID] [PMCID]

[33] Liu Z, Wang J, Xu Y, Guo M, Mi K, Xu R, et al. Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2. arXiv preprint arXiv:2004.04874. 2020. https://arxiv.org/abs/2004.04874v1

[34] Karow J. First epigenetic signature test for inherited disorders to launch in the US, Europe [Internet]. 2019 [Updated 2019 April 1]. Available from: https://www.mountsinai.org/about/newsroom/2019/first-epigenetic-signature-test-for-inherited-disorders-to-launch-in-the-us-europe-julia-karow

[35] Diagenode. Epigenetics and Coronavirus. [Internet]. 2020. Available from: https://www.diagenode.com/en/areas/coronavirus#:~:text=Mount%20Sinai's%20Icahn%20School%20of,pathogenic%20mutations%20and%20benign%20variants.

[36] Yi PS, Melnyk M, Pogribna IP, Pogribny RJ, Hine RJ, James SJ. Increase in plasma homocysteine associated with parallel increases in plasma S-adenosylhomocysteine and lymphocyte DNA hypomethyla-tion. J Biol Chem. 2000; 275 (38):29318-23. [DOI:10.1074/jbc.M002725200] [PMID]

[37] Choi SW, Friso S. Epigenetics: A new bridge between nutrition and health. Adv Nutr. 2010; 1(1):8-16. [DOI:10.3945/an.110.1004] [PMID] [PMCID]

[38] Bermejo LM, Aparicio A, Andrés P, López-Sobaler AM, Ortega RM. The influence of fruit and vegetable intake on the nutritional status and plasma homocysteine levels of institutionalised elderly people. Public Health Nutr. 2007; 10(3):266-72. [DOI:10.1017/S1368980007246580] [PMID]

[39] Brevik A, Vollset SE, Tell GS, Refsum H, Ueland PM, Loeken EB, et al. Plasma concentration of folate as a biomarker for the intake of fruit and vegetables: The Hordaland Homocysteine Study. Am J Clin Nutr. 2005; 81(2):434-9. [DOI:10.1093/ajcn.81.2.434] [PMID]

[40] Chen ZX, Riggs AD. DNA methylation and demethylation in mammals. J Biol Chem. 2011; 286(21):18347-53. [DOI:10.1074/jbc.R110.205286] [PMID] [PMCID]

[41] Kitagawa Y, Ohkura N. Autoimmunity: Treating type-1 diabetes with an epigenetic drug. Elife. 2014; 3:e05720. [DOI:10.7554/eLife.05720] [PMID] [PMCID]

[42] Fu W, Farache J, Clardy SM, Hattori K, Mander P, Lee K, et al. Epigenetic modulation of type-1 diabetes via a dual effect on pancreatic macrophages and β cells. Elife. 2014; 3:e04631. [DOI:10.7554/eLife.04631] [PMID] [PMCID]

[43] Mao Y, Mohan R, Zhang S, Tang X. MicroRNAs as pharmacological targetsin diabetes. Pharmacol Res. 2013; 75:37-47. [DOI:10.1016/j.phrs.2013.06.005] [PMID] [PMCID]

[44] Henaoui I, Stoll L, Tugay K, Regazzi R. Therapeutic potential of miRNAs in diabetes mellitus. Expert Rev Endocrinol Metab. 2015; 10(3):285-96. [DOI:10.1586/17446651.2015.996131] [PMID]

[45] Vester B, Wengel J. LNA (locked nucleic acid): High-affinity targeting of complementary RNA and DNA. Biochemistry. 2004; 43(42):13233-41. [DOI:10.1021/bi0485732] [PMID]

[46] Orom UA, Kauppinen S, Lund AH. LNA-modified oligonucleotidesmediate specific inhibition of microRNA function. Gene. 2006; 372:137-41. [DOI:10.1016/j.gene.2005.12.031] [PMID]

[47] Putta S, Lanting L, Sun G, Lawson G, Kato M, Natarajan R. Inhibiting microRNA- 192 ameliorates renal fibrosis in diabetic nephropathy. J Am Soc Nephrol. 2012; 23(3):458-69. [DOI:10.1681/ASN.2011050485] [PMID] [PMCID]

[48] Atlante S, Mongelli A, Barbi V, Martelli F, Farsetti A, Gaetano C. The epigenetic implication in coronavirus infection and therapy. Clin Epigenetics. 2020; 12(1):156. [DOI:10.1186/s13148-020-00946-x] [PMID] [PMCID]

[49] Bramswig NC, Kaestner KH. Epigenetics and diabetes treatment: An unrealized promise? Trends Endocrinol Metab. 2012; 23(6):286-91. [DOI:10.1016/j.tem.2012.02.002] [PMID] [PMCID]

[50] Xu Z, Tong Q, Zhang Z, Wang S, Zheng Y, Liu Q, et al. Inhibition of HDAC3 prevents diabe-tic cardiomyopathy in OVE26 mice via epigenetic regulation of DUSP5-ERK1/2 pathway.Clin Sci (Lond). 2017; 131(15)1841-57. [DOI:10.1042/CS20170064] [PMID] [PMCID]

[51] Eckschlager T, Plch J, Stiborova M, Hrabeta J. Histone deacetylase inhibitors as anticancer drugs. Int J Mol Sci. 2017; 18(7):1414. [DOI:10.3390/ijms18071414] [PMID] [PMCID]

[52] Weisbeck A, Jansen RJ. Nutrients and the pancreas: An epigenetic perspective. Nutrients. 2017; 9(3):283. [DOI:10.3390/nu9030283] [PMID] [PMCID]

[53] Bishop KS, Ferguson LR. The interaction between epigenetics, nutrition and the development of cancer. Nutrients. 2015; 7(2):922-47. [DOI:10.3390/nu7020922] [PMID] [PMCID]

This Page Intentionally Left Blank