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Modulation of host epigenome by coronavirus infections and developing treatment modalities for COVID-19 beyond genetics

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Abstract. – The recent Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) outbreak has resulted in coronavirus disease 2019 (COVID-19) pandemic worldwide, affecting millions of lives. Although vaccines are presently made available, and vaccination drive is in progress to immunize a larger population; still the risk of SARS-CoV-2 infection and related mortality is persistent amid threats of the third wave of the ongoing pandemic. In the scenario of unavailabil-

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ity of robust and efficient treatment modalities, it becomes essential to understand the mechanism of action of the virus and deeply study the molecular mechanisms (both at the virus level and the host level) underlying the infection processes. Recent studies have shown that coronaviruses (CoVs) cause-specific epigenetic changes in the host cells to create a conducive microenvironment for replicating, assembling, and spreading. Epigenetic mechanisms can contribute to various aspects of the SARS-CoV-2 multiplication cycle, like expressing cytokine genes, viral receptor ACE2, and implicating different histone modifications. For SARS-CoV-2 infection, viral proteins are physically associated with various host proteins resulting in numerous interactions between epigenetic enzymes (i.e., histone deacetylases, bromodomain-containing proteins). The involvement of epigenetic mechanisms in the virus life cycle and the host immune responses to control infection result in epigenetic factors recognized as emerging prognostic COVID-19 biomarkers and epigenetic modulators as robust therapeutic targets to curb COVID-19. Therefore, this narrative review aimed to summarize and discuss the various epigenetic mechanisms that control gene expression and how these mechanisms are altered in the host cells during coronavirus infection. We also discuss the opportunities to exploit these epigenetic changes as therapeutic targets for SARS-CoV-2 infection. Epigenetic alterations and regulation play a pivotal role at various levels of coronavirus infection: entry, replication/transcription, and the process of maturation of viral proteins. Coronaviruses modulate the host epigenome to escape the host immune mechanisms. Therefore, host epigenetic alterations induced by CoVs can be considered to develop targeted therapies for COVID-19.

Key Words:
Coronavirus, COVID-19, SARS-CoV-2, Epigenetics, Epigenetic regulation, Methylation, Therapeutic targets.

Introduction

Coronaviruses (CoVs) can infect both humans and animals. Several past outbreaks have been due to the emergence of CoVs, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) strains. Most recently, the SARS-CoV-2 outbreak originated in Wuhan, China, in December 2019. SARS-CoV-2 is a highly contagious resulting in a range of clinical symptoms causing coronavirus disease-19 (COVID-19), affecting multiple organs and systems of the body[1-4]. Due to high transmission rates, it spread in almost all the countries in the world with more than 225 million cases of COVID-19 and over 4.6 million loss of lives, as of September 12, 2021, as reported by the World Health Organization (WHO)[5]. Being a devastating pandemic of the 21st century, rapid advances in research paved the way in developing various kinds of effective COVID-19 vaccines by using different vaccine platforms, and vaccination programs are currently in progress for immunizing the global population at large, while other vaccines are also in the pipeline[6-9]. Few challenges, such as vaccine hesitancy, diplomacy, equitable access of vaccines to all the countries, the risks posed by emerging SARS-CoV-2 variants in affecting vaccine efficacy adversely and vaccinated people being infected despite vaccination are needed to be addressed appropriately[10-12].

Apart from these issues, the animal spillover events, cross-species jumping, zooanthroponotic potential and zoonotic concerns of SARS-CoV-2 need thorough investigations along with one health approach to be strengthened to tackle ongoing COVID-19 pandemic and future pandemics[13-17]. Though various drugs, therapies, and immunomodulatory agents have been recognized for use in emergency conditions to ameliorate the severity of COVID-19 in patients, the choice of curative drugs and medicines is yet to be discovered1[1,18-21]. It was found that SARS-CoV-2 has 96.2% similarity with the genetic formation of Bat-CoV-RaTG13 and this analogous property indicates the ancestral relevance between them2[2]. Emerging evidence suggests that the SARS-CoV-2 infection involves an interplay of genetic and epigenetic modulation in the host cells favoring the establishment and spread of the infection. Epigenetic alterations and regulations of the chromatin are important in maintaining cellular homeostasis by controlling the expression of the genes temporally and spatially. Epigenetic alterations have been reported to play essential roles in viral infections. Post-translational modifications at different chromatic, DNA, and RNA levels are the epigenetic modulation and control of gene expression. These post-translational modifications include methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. The epigenetic changes occur at the gene locus without modifying the nucleotide sequence of the gene.

DNA methylation involves adding methyl groups to the C-5 position of the cytosine ring in the DNA. DNA methylations are carried out

by a special class of methyltransferases called DNA methyltransferases (DNMTs). The DNA methyltransferase family includes five members: DNMT1, DNMT2, DNMT3A, DNMT3B and DNMT3L. DNMT1 acts on the hemimethylated DNA (important in DNA replication) while DNMT3A and DNMT3B act on unmethylated CpG dinucleotides (important in de novo methylation)[23]. Increased level of DNA methyltransferase is keenly involved with viral latency regulation, which functions by altering host cells' epigenetic structure[22]. DNA methylation is pivotal in cellular developmental processes, ageing, gene imprinting, X chromosome inactivation, gene silencing, and most importantly, maintaining genomic stability[23,24]. The DNA molecule is packed inside the nucleus by the histone proteins to form the chromatin fiber surrounded by histone proteins (nucleosomes). Post-translational modifications on the histones of the nucleosomes regulate the accessibility of the chromatin to the transcription factors and other regulators of gene expression and hence control the gene expression levels2[5-29]. Besides DNA and histone proteins, RNA also undergoes chemical modifications to regulate gene expression[30-32]. These modifications in the RNA are the basis of RNA interference[33], and show a tissue-specific distribution, resulting in a new field of RNA-epigenetics or epitranscriptomics[34]. RNA modification/epitranscriptomics have pivotal roles in the study of viral infections. Recently, a high-resolution map of SARS-CoV-2 has been published by the Korea Centres for Disease Control and Prevention (KCDC)[35]. They have identified about 41 RNA modifications sites on the viral transcripts. The most frequent motif was AAGAA present throughout the viral genome. This internal modification to the poly(A) tail may increase the stability of the viral RNA and the efficiency of translation of viral structural and non-structural proteins. This mechanism may help the virus in invading the host immune mechanism[35,36].

Viruses have utilized epigenetic modifications in the host cells to establish an infection and/or to escape the host immunity. As obligatory intracellular parasites, viruses can develop many ways of taking over cellular processes to complete their life cycle and thus evading the immunity responses of host cells. Viruses causing persistent infectious diseases are mainly benefited from inherited epigenetic manipulations in host transcription, which generate an environment for the persistent state without continuous expression of initiating effectors[37]. The host response genes for cell cycle development, survival, senescence, immunity, and inflammation are major target candidates for such kind of epigenetic regulation and control[38]. The present narrative review discusses the various epigenetic alterations that occur in the host cells due to coronavirus infections and how these modifications can be targeted to develop treatment modalities for COVID-19.

Epigenetic Mechanisms: the Key Players

Epigenetics involves the study of phenotypic changes caused without any alterations in the DNA nucleotide sequence. The fundamental mechanism of epigenetic is that gene expression initiates through the chemical composition alteration of DNA bases and modification in the chromosomal construction, which takes place within the DNA[39]. In recent years, epigenetics has advanced tremendously, and researchers deciphered the dynamics of epigenetic regulations that affect the chromatin structure and function, leading to alterations in the host gene expression patterns.

Epigenetic regulations play pivotal roles in modulating cellular pathways critical in several physiological and developmental processes, such as embryonic development, memory function, immunity, and various diseases[40,41]. Unlike mutations that alter the nucleotide sequence, epigenetic changes alter the chromatin structure without altering the nucleotide sequences/genetic codes. Therefore, epigenetic modifications are reversible and result from the gene-environment interactions suggesting that changes in the phenotypes are due to mutations and interaction between genes and the environment[40]. Recent years[42,43] have witnessed rapid development in epigenetic research, which has gained importance in studies related to cancer biology, immunity, and infectious diseases. Studies have confirmed that several DNA viruses and some RNA viruses alienate the regulatory mechanism of the host epigenome, resulting in changes in the host genome expression profiles to create a conducive environment for the life cycle of the virus in the host (virus replication and spread)[44]. In a recent study, it was found that correspondence of T cell with the environmental state in both steady and diseases condition is vigorously provoked by the gene regulatory system. On the other hand, DNA methylation was quite different in the children compared to the aged people, suggesting the association of ageing with T cell epigenomes[45].

In the past years, the techniques for studying

epigenetics have seen dramatic advancements. Therefore, these techniques can be utilized to study and understand the exact role of epigenetic changes underlying developmental processes, immunity, oncological processes, and infectious diseases[46,47]. A detailed map of the human genome and epigenome was available to the research community with the completion of the human genome project in 2003[48]. This followed revolutions in sequencing techniques and the evolution of next-generation sequencing (NGS) technology. Epigenetic studies utilized the NGS platforms and principles to refine epigenetic techniques, such as ChIP-Seq, RNA-Seqand MeDIP-Seq[49,50]. These techniques can be used to study the epigenetic changes at the genome level, such as alterations in DNA methylation, histone modificationand DNA-protein interactions. These epigenetic techniques, such as Epigenome-wide association studies (EWAS), have enabled the study of the association of epigenetic changes with disease phenotypes[51]. EWAS studies[51,52] can provide novel epigenetic markers associated with disease phenotypes and various pathological and non-pathological conditions[51,52]. It is important to understand the genomic organization in eukaryotic cells to understand how viruses modulate the host epigenetic machinery for establishment of the infection and escape host immunity,

Chromatin

Chromosomes and mitochondrial DNA store the genomic information in the nucleotide sequences. The formation is based on interplay between two vital criteria, namely polymer biophysics and biochemical interactions[53]. Chromosomes are found in highly condensed deoxyribonucleoprotein complexes called chromatin in the nucleus. Chromatin exists in two forms: euchromatin and heterochromatin. Heterochromatic regions are stained dark with Giemsa stain and are tightly packed and transcriptionally less active. On the other hand, euchromatin is highly stained with Giemsa, loosely packed, and transcriptionally more active[54].

Chromatin Organization

Histone proteins (H) are basic proteins that help in the condensation of the DNA into nucleosomes. Histone proteins play a vital role in the systemic and utilitarian aspect of conducting the altering operation between the activated and deactivated chromatin state[55]. The nucleosome is a tightly-packed histone octamer consisting of two H3, H4, H2A , and H2B copies at the core. There are three types of H3 histones, namely H3.3, H3.2 and H3.4, that play a significant regulatory role in the case of histone formation. H4 histones are highly conserved. H2A has a large number of variants that are mainly associated with the repair of damaged DNA. H2b histone also helps to organize the DNA of eukaryotic organisms[55]. Approximately 165 base pairs of DNA are wrapped around histone proteins' octamer, giving beads on a thread-like structure. The nucleosome structure is important as it provides stability to the DNA molecule by tight packaging with histone proteins, regulates DNA replication, distributes daughter cells during cell division, and regulates the binding of transcription factors and regulatory proteins with the DNA to regulate the gene expression[56].

Post-translational modifications in the N-termini of the histone proteins (lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, lysine ubiquitination and sumoylation) result in epigenetic conformational changes in the chromatin and altered the expression of associated genes5[6,57]. According to the "Histone Code" reported in 2001 there exists a specific coding pattern in the chromatin-mediated by chemical alterations in the histone tails[58]. Different modifications in the histone tails, indicating the C or N-terminal regions that flank the histone core, result in binding with different chromatin-associated and other regulatory proteins, thus playing a pivotal role in chromatin signalling[59,60]. Any change in the histone code brought about by chemical alterations in the histone tails affect the recruitment of chromatin-associated proteins, leading to differential expression of associated genes. These changes at the chromatin level in histone modifications regulate several vital cellular processes, such as transcription, replication, post-translational changes and state of tissue differentiation[61,62].

Epigenetic Regulation/Modulation of Host Response

The innate immune system of the body responds to various stimuli differently. The differential response is mediated by changes in the expression levels of multiple genes of the immune response mechanisms in a cell and tissue-specific manner[63-65]. In this cascade of an immune response, epigenetic regulation of the expression of the genes involved is now a fact. Epigenetic factors are actively involved in the activation and

execution of the immune responses. The epigenetic regulation of the immune response involves regulating the expression and recruitment of transcription factors, regulating the expression of the mediators, and controlling the secondary gene programs6[5,66].

Interferons (IFNs) and tumor necrosis factors (TNF) are the most important genes that play pivotal roles in the innate immune system. These genes have poised promoters and are rapidly induced in response to a stimulus. The presence of CpG islands in the promoters of these genes makes them defiant to DNA methylation and histone tail modification. These epigenetic modifications are widespread in the promoters of highly active genes and have higher RNA Pol II recruitment[66]. However, the IFN stimulated genes show low levels of histone modifications, such as H3K4me3, H4Ac, and the promoters of these genes show low levels of RNA Pol II recruitment[67]. Therefore, these genes need additional transcription factors and chromatin remodelers, such as ATP-dependent chromatin remodelling complex SWItch/sucrose non-fermentable (SWI/SNF) to get activated and transcribed[44,64].

Dendritic cells and macrophages are the critical sensors of antigenic signals. Upon activation by the stimulus, these cells initiate a temporal and spatial response. The signals released from these cells should be highly specific for the cell types to make sure that the activation and initiation of the immune response are cell and stimulus-specific. The cell-specific signals released from the dendritic cells and macrophages are mediated by the expression and secretion of IFN and TNF. The capacity of the epigenome of these cells to quickly change according to the stimulus is essential for the activation and persistence of the host immune response. H3K9me2 histone modification has been shown to be associated with the levels of IFN *in vitro*. H3K9me2 induces DNA methylation and heterochromatinization and inhibits acetylation of histone tails by recruiting a transcriptional repressor of the heterochromatin protein 1 family[68]. The levels of H3K9me2 promoter methylation in the type I interferon genes are inversely associated with the expression of IFN specific genes in the dendritic cells. This observation reinforces the role of histone modifications in regulating the IFN response[68,69].

H3K4me3 histone modifications are enriched in the promoters of actively expressed TLRs. It has been shown that post one hour of lipopolysaccharide (LPS) induced stimulation of dendritic cells and macrophages; there was a marked increase in the overall histone acetylation and polymerase II (Pol II) recruitment at the specific promoters[70]. These findings signify the vital role of histone modifications in activating and executing innate immune responses.

Epigenetic Alterations by Coronaviruses

Epigenetic mechanisms can contribute to a number of different aspects of the SARS-CoV-2 multiplication cycle, like expressing cytokine genes, viral receptor ACE2, and implicating different histone modifications in COVID-19. Over the SARS-CoV-2 infection duration, proteins are physically associated with various host proteins, resulting in many interactions between epigenetic enzymes and virus proteins[66]. Affinity purification mass spectrometric analysis was carried out to study 26 SARS-CoV-2 proteins to inspect the protein interactions between host enzyme and virus proteins[67]. Precisely, 332 human proteins were found as binding partners for proteins of SARS-CoV-2. Among these, eight are considered epigenetic modulating agents. Notable interactions were demonstrated between human BRD2-BRD4 and viral E protein, human HDAC2 and viral NSP5, and human CUL2 complex and viral ORF10[67].

The INFs mainly mediate the establishment of an antiviral state in the host by initiating the virus-mediated host immune response by activating the IFN stimulated genes[71,72]. Many viruses have evolved various antagonistic mechanisms to escape or fight the IFN specific gene effectors[73]. The IFN pathway and the innate immune response mechanism are controlled by epigenetic regulation mediated by epigenetic modifications such as histone methylations, manipulation of the enzymes involved in histone modification, DNA methylation, and chromatin remodelling. Viruses interfere with these epigenetic processes and encode specific viral proteins that directly interact with modified histones of the host[65,74-76].

The H3N2 influenza A virus establishes the infection by inhibiting the host innate immune response initiation by modifying the epigenetic regulation of host gene expression. It uses the histone mimicry tool to manipulate the host immune response. It has been reported[77] that the carboxy terminus of the viral H3N2 nonstructural protein NS1 has sequence homology with the host amino terminus of the histone H3 tail. Therefore, the viral NS1 protein mimics the H3 histone tail and thereby lures the transcription

complex and inhibits its docking to the H3K4, consequently inhibits the initiation of INF stimulated genes[77,78].

Alterations in the expression pattern of IFN stimulated genes by pathogenic influenza viruses and coronaviruses have been reported in a human airway epithelial cell line (Calu3 cells)[79]. The Calu3 cells showed several virus-specific IFN stimulated gene expression signatures upon infection with different respiratory viruses. The pathogenic H5N1 avian influenza A (HPIA) virus altered the expression pattern of the IFN stimulated genes even after 7 hours of infection. However, the 2009 pandemic H1N1 strain did not modulate the IFN stimulated gene expression and the infected Calu3 cells induced an antiviral state at 3 hours post-infection. SARS-CoV infected Calu3 cells showed elevated expression of IFN stimulated genes, but the response was delayed and observed at 24 to 48 hours post-infection. MERS-CoV infection also showed considerable inhibition, and a delayed IFN stimulated genes expression was observed at 18 hours post-infection[79]. These observations indicate that the virus employs an antagonistic mechanism to epigenetically manipulate the INF-mediated antiviral innate host immune response and establishes a successful infection[80].

It has been shown that the promoters of the IFN stimulated genes have higher H3K4me marks (activating) compared to the repressive H3K27me3 marks that favor euchromatinization and active transcription of IFN stimulated genes during H1N1-2009 and SARS-CoV infection[81]. However, HPAI and MERS-CoV infected Calu3 cells have shown elevated levels of H3K27me3 and decreased levels of H3K4me3 in the promoters specific IFN stimulated genes; hence, their expression is repressed. This demonstrates that these viruses utilize antagonistic mechanisms to manipulate the IFN mediated host innate immunity[81]. DNA methylation process corresponding to 44 CpG positions was found to have an association with the clinical emergency of COVID-19, and 23 of them were located in 20 annotated coding genes. While studying these genes, it was identified that a few of them, including the inflammasome component, were missing in Melanoma-2 and the major histocompatibility complex class 1 molecule and caused disruption to the immune response by intervening in the regulation of interferons[82]. Another study[83] found that two of the genes, namely HSPA1L and ULBP2, were associated with upregulation in AZA-treated lung epithelial cells and immune cells, which indicates their epigenetic regulation during the respiratory infection caused by SARS-CoV-2.

Epigenetic Alterations at Host Cell Entry Level

ACE2 is the surface molecule present on the host cells and mediates the interaction of the viral spike protein with the host cells, enabling the entry of SARS-CoV-2 in the host cells. Since ACE2 is expressed in a vast population of cells, such as the cells of the lower respiratory tract, oesophagus, kidney, bladder urothelial cells, absorptive enterocytes, cardiomyocytes, and cholangiocytes, the SARS-CoV-2 infection is not restricted to the respiratory system but also results in illnesses in other organ systems[84]. Sirtuins are a family of deacetylases that help in the maintenance of cellular homeostasis[85]. Silent information regulator T1 (SIRT1), an HDAC class III molecule, has been reported to regulate ACE2 expression levels by binding to its promoter[86]. It has not been shown that SIRT1 increases the entry of SARS-CoV-2 into the host cells by increasing ACE2 expression. However, it has been observed that COVID-19 patients expressing higher levels of ACE2 show a better prognosis, probably because of decreased hyper inflammation[87-89]. It has been reported that SIRT1 affects the entry of SARS-CoV and HCoV-NL63 into the host cells. These viruses utilize ACE2 for entry into the host cells[90].

Recently, T cells of lupus patients have been reported to upregulate ACE2, which is tightly regulated by DNA methylation. This may lead to the poor prognosis of the SARS-CoV-2 infection. Moreover, the genetic sequence ACE2 encoding gene on the X chromosome was prone to epigenetic changes. The epigenetic changes in the ACE2 gene were mediated by multiple CpG sites situated in the ACE2 promoter region upstream of the transcription start site. Intriguingly, oxidative damage associated with viral infections can exacerbate DNA methylation deficiency, resulting in greater ACE2 hypomethylation and increased viremia. As a result, hypomethylation and overexpression of ACE2 in T cells may enhance viral infections and viral dispersion, increasing vulnerability to COVID-19. According to their findings, epigenetic imbalance may increase the likelihood and morbidity of SARS-CoV-2 infection in lupus patients[91].

There are several other host cell receptors,

such as aminopeptidase N (APN), dipeptidyl peptidase 4 (DPP4), and 9-O-acetylated sialic acid used by HCoV-229E, MERS-CoV, HCoV-OC43 and HCoV-HKU1, respectively[92-95]. Promoter hypermethylation causes downregulation of APN gene expression, and its expression is increased by azacitidine (5-azaC)[95,96]. The HDAC inhibitor CHR3996 and the APN inhibitor tosedostat synergistically activate NF-kB in melanoma cells[97]. Glucocorticoids upon binding to the promoter have been reported to epigenetically upregulate DPP4 gene expression in macrophages[98]. Therefore, these molecules can be tested as epigenetic treatment strategies to control the cell surface receptors for SARS-CoV-2.

Epigenetic Alterations During Viral Replication and Transcription

Coronaviruses, like any other virus, employ a multi-enzyme unit for replication. The RdRp/Nsp12 enzyme and its co-factors Nsp7 and Nsp8 play an essential role in viral RNA replication and transcription of SARS-CoV-2[99]. This is brought about by the interaction of Nsp7 with the 7SK small nuclear ribonucleoprotein (7SK snRNP) complex. The 7SK snRNP complex consists of La-related protein (LARP7), methyl-phosphate capping enzyme (MEPCE), and hexamethylene bisacetamide inducible protein (HEXIM1). The 7SK snRNP complex has been reported to sequester positive transcription elongation factor (P-TEFb), which plays an important role in viral replication[100,101]. Another co-factor, the Nsp14, an exonuclease, is also vital for coronavirus RNA synthesis[102]. Nsp14 regulates several metabolic pathways by interacting with SIRT5. It has deacetylase, desuccinylaseand demalonylase activities[103]. The Nsp13 helicase/triphosphatase helps release nascent RNA strand, followed by the generation of new viral particles[104]. Nsp13 might be under the control of coactivator proteins such as p300, which is under the control of HDACs[105]. Therefore, the inhibition of HDACs might inhibit the coronavirus replication by inhibiting p300 and ultimately inhibiting the Nsp13 essential in releasing the newly synthesized RNA. Nsp4, another molecule in the viral RNA replicationalso interacts with HDAC2; thus, epigenetic therapies targeting the inhibition of HDAC2 can control the viral RNA replication by modulating the functions of Nsp4[106]. Nsp16 plays an important role in the post-transcriptional modification of the viral RNA. Methyltransferase inhibitors can be used to inhibit the Nsp16 methyltransferase activity, thereby regulating the viral RNA post-transcriptional modification[107]. A thorough study on HIV-1 revealed that $CD4^+$ T cell increases the expression of DNMT and initiate hypermethylation of individual cellular promoters. On the contrary, demethylation of FOXP3 promoter was observed on the sample of blood mononuclear cells and colon cells associated with the downregulation of DNMT[108].

Epigenetic Alterations During Coronavirus Protein Maturation

The 3C-like protease ($3CL^{pro}$) and the papain-like protease (PL^{pro}) are the important enzymes that mediate the cleavage of the newly synthesized viral polyproteins[109]. These enzymes cut the polyprotein at different cleavage sites, resulting in 16 Nsps in the virus (SARS-CoV and MERS-CoV)[106]. Nsp5 is a non-structural protein produced by SARS-CoV-2, which has the function of cleaving viral polyprotein[110]. HDAC2 is a protein found in the human, which activates the immune system to act against viral particles. HDAC2 contains a binding site for Nsp5, which inactivates the protein and causes deactivation of immune responses[111]. HDAC2 and tRNA methyltransferase 1 (TRMT1) are actively cleaved by 3CLpro[106]. This signifies that the 3CLpro acts as a molecular mimic of HDAC2 inhibitor and, therefore, it can regulate the gene expression in the infected cells in response to viral infection. The tRNA modifications induced by TRMT1 are essential for ensuring protection against oxidative stress in the cells[112]. Since TRMT1 is cleaved by $3CL^{pro}$, an important enzyme of SARS-CoV-2, $3CL^{pro}$ might cause an imbalance in the cellular redox homeostasis. There are several drugs, including lopinavir, that can inhibit $3CL^{pro}$[113]. Besides these crucial enzymes, SARS-CoV-2 has several structural viral proteins such as NP, M, Eand S that help generate new infectious virions. Resveratrol treatment activates SIRT1 in the infected cells, resulting in decreased viral replication[114]. Two different strategies can be employed to block the maturation of SARS-CoV-2 structural proteins: by using SARS-CoV-2 protease inhibitors to inhibit the cleavage of viral polyprotein by $3CL^{pro}$ and PLpro using epigenetic treatment strategies to decrease the expression level and activity of structural proteins[115-117]. In addition to that, 9654 number of mutations are observed in the spike protein compared to reference spike protein sequences[118].

Epigenetic Regulation of ACE-2 and

TMPRSS2: Effect on the Expression of These Receptors

It has been shown that the expression of ACE2 is controlled epigenetically[119]. Techniques following RT-qPCR and single-cell RNA sequencing had divulged multiple tissues associated with ACE2 expression1[20]. Non-ISGs, which are analogous to IL-6 and ACE2, have been observed to alter the chromatin accessibility through histone modifications and accumulation of transcription factor, such as PU.1, IRF and NF-κB. These epigenetic changes stigate more increased ACE2 expressionleading to a respiratory and inflammatory response in the context of COVID-19[121]. A recent study[122] has shown that among the studied cell types, the promoter methylation of ACE2 was the lowest in the lung epithelial cells. Thus, the expression levels of ACE2 are high in these cells. The methylation of ACE2 has been found to correlate well with gender and age and plays a vital role in COVID-19 disease[122,123]. Another exhaustive study, including 700 lung transcriptome samples highlighted the overexpression of ACE2 in lung tissues[123]. In another study, ACE2 gene was hypermethylated in the respiratory tissues of children[122]. This can explain why older adults are more susceptible to SARS-CoV-2 infection.

TMPRSS2, an androgen receptor signalling molecule, also help SARS-CoV-2 to enter into the host cell and spread the infection. During SARS-CoV-2 infection, TMPRSS2 primes the viral spike proteins by inducing their cleavage and thus help in viral entry by facilitating the fusion of viral and host cell membranes[124,125]. It has been reported that DNA methylation influences the expression of TMPRSS2[126]. It is highly expressed in the lung epithelial cells compared to other cell types of the lung[127]. Therefore, TMPRSS2 can be targeted epigenetically to inhibit the establishment of SARS-CoV-2 infection.

The epigenetic and genetic variations of ACE2 are crucial to understanding the pathobiology and developing therapeutic and preventive approaches. In this context, Kianmehr and coworkers[122] have highlighted the importance of genetic and epigenetic variations of the ACE2 receptor for COVID-19. Acute hyper inflammation is crucial in COVID-19 disease progression and severity and is the main reason for COVID-19 related deaths. In particular, in lung cancer patients, the COVID-19 severity is significantly observed and may be due to the commonly involved genes (TMPRSS2, ACE2, PAI-1 and furin). Moreover, the overall inflammatory responses are affected by a series of reversible epigenetic modifications. Hence, it is highly recommended to understand the epigenetic regulation of inflammation, which may help develop potentially novel strategies to prevent, diagnose and treat such diseases[128].

In a case-control study using saliva samples, there was no statistically significant difference in the methylation and expression levels of ACE2 and TMPRSS2 between the cases and the controls. However, ACE2 expression negatively correlated with ACE2 methylation. Also, no significant correlation between TMPRSS2 expressionand TMPRSS2 methylation was observed. There was a positive association between the expression of ACE2 and TMPRSS2. However, no association between the methylation status of ACE2 and TMPRSS2 was seen. Furthermore, no correlation was observed between the expression and methylation levels of ACE2 and TMPRSS2 and the clinical outcomes or symptoms[129].

Significance of Epigenetic Alterations in COVID-19 and Potential in Therapy and Management

Considering the notable contribution of epigenetic mechanisms in regulating many aspects of COVID-19, epigenetic enzymes can be targeted as prospective therapeutic approaches. Numerous clinical trials have focused on epigenetic mechanisms for the treatment of COVID-19, and many trials with other strategies are also in progress. One clinical trial (NCT04403386) exploits biomarkers for immune cell profiles, smokingand DNA methylation patterns. This investigation determined a high-risk threat from virus-induced mortality and morbidity experienced by smokers than that of non-smokers since smoking is likely to change epigenetic signatures[130]. Another study[131] (NCT04411563) comprehends the correlation between the severity of COVID-19 and related epigenetic biomarkers, such as epigenetic signatures and microRNAs. Epigenetic research has provided sufficient evidence that viruses have evolved mechanisms that antagonize the host epigenetic regulatory machinery to create a conducive host environment for replicating the viral genome and spreading the infection. Modulation of the host epigenetic mechanisms by the virus alters the host cell transcriptome, thereby establishing the viral infection in the host cells[44,132]. Genes are expressed in a time-specific and tissue-specific manner. It has been reported[133,134] that with advancing age, epigenome changes compromise host immunity by altering immune cells and

adaptive host immunity. This compromises the host defense mechanisms against viral infections. It is well documented that the coronaviruses MERS-CoV and SARS-CoV-1 antagonize the host antigen presentation or activate IFN genes by altering the host epigenome[79,135].

The vulnerability of the aged people to SARS-CoV-2 infection may be explained by the age-related epigenetic changes (DNA methylation) in the host immune cells that enablesthe virus to enter and establish infections in the elder people[133,136]. Several treatment strategies for COVID-19 have been tried, and some others are under investigation[11,18-21,106,137-140]. Several clinical trials[111,141] based on FDA approved agents that target epigenetic mechanisms and antiviral and epigenetic drugs, in combination, are currently being done to establish important inhibitors of viral replication and regulate the host immune response. The fact that antiviral drugs' pharmacokinetics and pharmacodynamic characteristics may also be affected by epigenetic modulation, epigenetics is much relevant to consider while designing treatment strategies for SARS-CoV-2 infection[142].

A review[141] recently summarized the epigenetic mechanisms having a role in coronavirus infections and summarized the epigenetic therapeutic targets. As discussed in earlier sections, several classes of HDACs regulate the nonstructural proteins governing the viral life cycle in the host (viral transcription, replication, and maturation). These observations indicate that various HDAC inhibitors (Vorinostat or suberanilohydroxamic acid (SAHA), combined with antivirals) can be investigated for their potential in interfering with the viral life cycle[143-145]. It is important to remember that HDAC inhibitors like vorinostat (SAHA), romidepsin, panobinostatand belinostat have been authorised by the US Food and Drug Administration as anti-cancer medicines for certain cancer types. Many more are being tested for various cancers in the pre-clinical and clinical phases[145-148]. HDAC inhibitors thus have well-proven therapeutic potential and clinical use. Hence, it is urgent to explore the therapeutic potential of available HDAC inhibitors against COVID-19 (Figure 1).

Since ACE2 expression is under tight epigen-

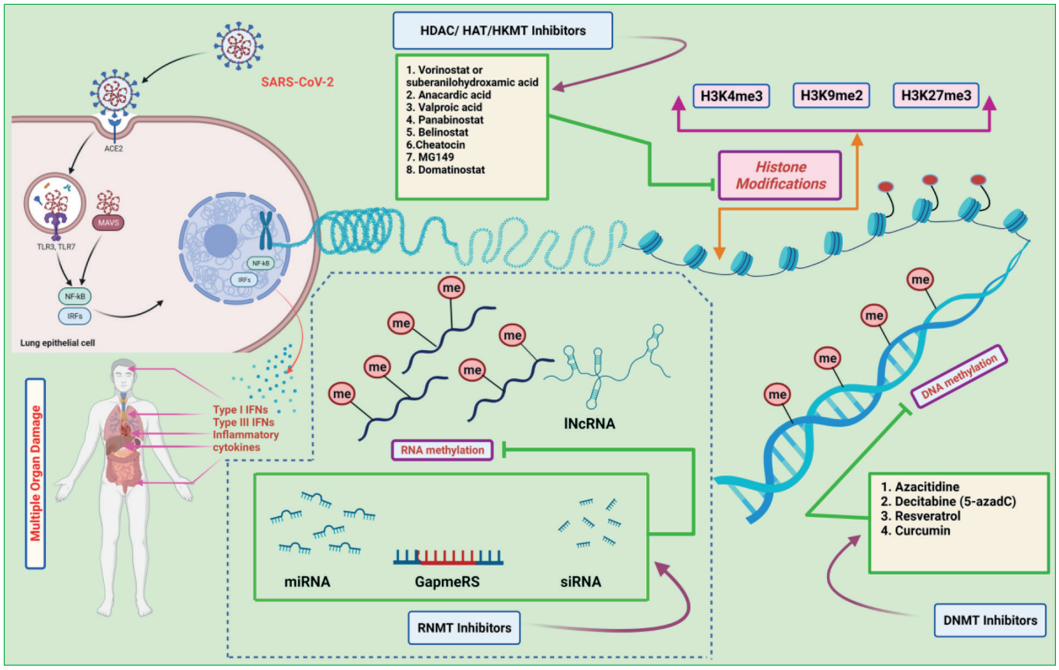

Figure 1. Epigenetic changes and possible therapeutic interventions for controlling epigenetic alterations in SARS-CoV-2 infection. Epigenetic markers such as chromatin remodelling, histone modification, DNA, and RNA methylation all have a role in the immunological response. The figure represents the regulation of various epigenetic changes such as DNA, RNA methylation, and histone modifications by exploiting inhibitors of HDAC, DNMT, and HMT. Inhibiting certain epigenetic mechanisms reduces viral replication, making it an important treatment approach for coronavirus infected individuals. Epigenomics is a valuable approach for discovering new ways to limit, mitigate, or reverse the viral infection. The enzymes that cause epigenetic changes might be used as prospective candidates for novel antiviral medicines. *Abbreviations*: HDAC: Histone deacetylases; HAT: Histone acetyltransferase; HKMT: Histone methyltransferase; DNMT: DNA methyltransferases; RNMT: RNA methyltransferase. The figure was designed by the Biorender.com program (https://biorender.com/, accessed on 30 June 2021).

etic regulation by the enzymes, such as DNMT1, histone acetyltransferase 1 (HAT1), histone deacetylase 2, the inhibition of these enzymes by the specific inhibitors (DNMT1 inhibitors: Azacitidine; HAT1 inhibitors: anacardic acid; HDAC2 inhibitors: valproic acid) may be used for controlling coronavirus infections1[06,139,149-151] (Figure 1). Also, the already established epigenetic drugs used in cancer treatment can be evaluated for their anti-inflammatory and antiviral potential[141,152]. The polycomb repressive complex 2 (PRC2), which causes H3K27me3 in the ISGs, is being tested as pharmacological target for cancer control. Clinical trials are ongoing to test the pharmacological inhibitors of PRC2 in cancer treatment. This can also be repurposed to manage COVID-19[153].

Cytokine storm characterized by over-expression of inflammatory mediators is highly implicated in the multi-organ failure and mortality in COVID-19[140,154]. Decitabine [5-aza-2-deoxycytidine (5-azadC)] is a DNMT inhibitor and has been reported to cause inhibition of DNA methylation in macrophages. Thus, Decitabine suppresses inflammatory responses in the macrophages1[41]. One ongoing clinical trial aims to evaluate Decitabine as a treatment modality in ARDS treatment (CTI: NCT04482621).

Studies[155,156] have shown that immune cells possess an epigenetic memory, called Trained Immunity (TRIM), for primary infection through epigenetic reprogramming. The primary infection/exposure enables the innate immune cells to develop an epigenetic memory for the infection and elicit an enhanced immune response to the second exposure[157]. In a study, it has been observed that β-glucan-driven TRIM involves epigenetic reprogramming. This strategy can be used in COVIID-19 treatment1[57]. In a recent study, peripheral blood mononuclear cells from people recovering from COVID-19 and healthy volunteers were analysed for single-cell chromatin accessibility and T cell receptors. In the patients recovering from COVID-19, chromatin modification was seen in both innate and adaptive immune cells. TBET-enriched CD16+ and IRF1-enriched CD14+ monocytes with successive trained and activated epigenomic states were prevalent in recovered patients compared to healthy volunteers. The B-cell lineages in recovered people progressed quickly from immature B cells to antibody-producing plasma cells. Additionally, combining single-cell T cell-receptor clonality with the chromatin accessibility landscape indicated the proliferation of potential SARS-CoV-2-specific CD8+ T cells exhibiting epigenomic profiles, which favour effector or memory cell development. Overall, the findings show that immune cells recovering from COVID-19 have global chromatin accessibility landscape remodelling, indicating the formation of immunological memory[158].

Studies[159-162] have proposed that using natural products and vitamins (e.g., Vitamin D and quercetin) can reduce the expression of ACE2, inflammatory response (cytokine storm) and boost immunity to COVID-19. Curcumin, 8-hydroxyquinolones, and sulforaphane are other possible natural compounds that might cause epigenetic silencing of the ACE2 gene, thereby preventing SARS-CoV-2 infection[149,162]. Resveratrol, selenium, isothiocyanates, such as sulforafan, tea polyphenols, curcumin, quercetin, genistein, anthocyanins, indole-3-carbinol and withaferin A might be effective for the treatment of several diseases through epigenetic mechanisms. These nutrients and bioactive dietary components may have an anti-SARS-CoV-2 and epigenetic effect on COVID-19 patients[163-166]. Thymoquinone is an active component of black seed oil, and possesses medicinal (antioxidant, antiviral, antimicrobial, anti-inflammatory, anticoagulant, and immunomodulatory) activities. Thymoquinone may increase the activity and number of cytokine suppressors, natural killer cells, lymphocytes, and macrophages. It has antiviral activity against hepatitis C virus, murine cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and also against the SARS-CoV-2 strain isolated from Egyptian patients. It is also reported that thymoquinone can modulate epigenetic machinery (DNA methylation and demethylation, histone acetylation and deacetylation), and may alter the genetic expression of non-coding RNAs (miRNA and lncRNA)1[67,168]. The use of *Nigella sativa* may be beneficial for treating COVID-19, which blocks the virus entry into pneumocytes, improves zinc intake, and prevents virus replication[169]. Moreover, TaibUVID nutritional supplements may help the rapid cure of SARS-CoV-2 infection1[70].

RNA-based molecular treatment strategies have also been proposed for COVID-19 treatment1[71,172]. RNA-based molecular treatment modalities work by epigenetically modulating the genes required for viral entry, replication, and maturation. The small interfering RNAs (siRNAs), microRNAs (miRNAs), and locked nucleic acid antisense oligonucleotides (LNA) targeting the 5′UTR regions of the Spike protein are proposed to be effective in both

preventing and treatment of COVID-192[0,173,175]. Recent research sought to anticipate mature miRNA (microRNA) sequences in the SARS-CoV-2 genome and their impact on protein-protein interactions in afflicted cells and gene-drug connections to identify potential therapeutic candidates. VMir analysis identified a total of 62 potential hairpins. MiRBoost identified three hairpin structures as genuine precursor miRNAs. In 100 SARS-CoV-2 viral genomes, five distinct alterations were discovered in precursor miRNA sequences. In precursor miRNAs, mutations modestly increased MFE values and entropy. In PANTHER, KEGG, and Wiki pathway analyses, gene ontology keywords related to fibrotic pathways and the immune system were shown to be enriched. A network of 60 genes was discovered using PPI analysis. SMAD1 was identified as a hub gene in the network using CytoHubba analysis. In SARS-CoV-2 infected A549 cells, the anticipated miRNA targets FAM214A, PPM1E, NUFIP2 and FAT4 were downregulated. MiRNAs in the SARS-CoV-2 viral genome have been shown to have a role in developing the COVID-19 disease by activating pathways linked to fibrosis in virus-infected cells and regulating the innate immune system. The SMAD1 protein, which plays an important role in TGF signalling[176], might connect both pathways. Further, deciphering these pathways and miRNAs can be exploited to develop effective therapeutic regimens.

Identifying COVID-19 *via* epigenetics would lead to a better knowledge of disease pathogenesis and therapeutic interventions[141]. Based on the epigenome-wide association study (EWAS) the interrelationships between respiratory failure and DNA methylation have been investigated[82]. Epigenetic biomarkers were compared in patients needing acute oxygen therapy to asymptomatic individuals who did not need oxygen therapy. In addition, the authors define EPICOVID, a DNA methylation-based signature that might aid in determining illness severity. Patients with COVID-19 were considered suitable if they did not have any of the following risk factors and comorbidities: obesity, diabetes, hypertension, autoimmune diseases, chronic cardiovascular or lung diseases, smoking habit, or old age (> 61 years), effectively limiting the EPICOVID signature's impact. When it came to ethnicity, the majority of the patients investigated belonged to the West-Eurasia group, according to the Human Origin Project's demographic stratification. The study only looked at DNA methylation sites, which is a restriction. Hence, a broader epigenetic approach that included histone acetylation, phosphorylation, ubiquitinylation, and sumoylation may have provided a complete picture of COVID-19's epigenetic landscape. Even with these biological, clinical, and cohort constraints, the EPICOVID signature may be beneficial in developing therapeutic interventions based on epigenetics[177].

Conclusions and Future Prospects

In summary, coronaviruses alter the host epigenome to establish successful infections and subsequent spread of the infection. Several layers of epigenetic regulation, like histone modifications and DNA methylation, play a role in determining the SARS-CoV-2 infection outcomes. Host cell mounts epigenetic mechanisms mediated more robust and effective immune response to eradicate virus infection. The viral particles attempt to escape from this response and reprogram the cell, creating an environment that promotes virus proliferation, new viral particles assembly, and reproduction to attack more cells. Epigenetic mechanisms are likely to play a role in various aspects of the SARS-CoV-2 multiplication cycle, like expressing cytokine genes, viral receptor ACE2, and implicating different histone modifications. Coronaviruses modulate the host epigenome to escape the host immune mechanisms. Several epigenetic modifications at the DNA, RNA, and histone levels have been reported that provide essential targets for therapies against coronavirus infections. Although vaccines are now available against COVID-19, they are not fully efficient against SARS-CoV-2 infection. Therefore, extensive epigenetic studies should be conducted to further explore the virus-induced epigenetic changes and target these epigenetic markers to develop antivirals for SARS-CoV-2.

Conflict of Interest

All authors declare that there is no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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Authors' Contribution

All the authors substantially contributed to the conception, compilation of data, checking and approving the final version of the manuscript, and agree to be accountable for its contents.

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