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Involvement of epigenetics in affecting host immunity during SARS-CoV-2 infection

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ABSTRACT

Coronavirus disease 19 (COVID-19) is caused by a highly contagious RNA virus Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), originated in December 2019 in Wuhan, China. Since then, it has become a global public health concern and leads the disease table with the highest mortality rate, highlighting the necessity for a thorough understanding of its biological properties. The intricate interaction between the virus and the host immune system gives rise to diverse implications of COVID-19. RNA viruses are known to hijack the host epigenetic mechanisms of immune cells to regulate antiviral defence. Epigenetics involves processes that alter gene expression without changing the DNA sequence, leading to heritable phenotypic changes. The epigenetic landscape consists of reversible modifications like chromatin remodelling, DNA/RNA methylation, and histone methylation/acetylation that regulates gene expression. The epigenetic machinery contributes to many aspects of SARS-CoV-2 pathogenesis, like global DNA methylation and receptor angiotensin-converting enzyme 2 (ACE2) methylation determines the viral entry inside the host, viral replication, and infection efficiency. Further, it is also reported to epigenetically regulate the expression of different host cytokines affecting antiviral response. The viral proteins of SARS-CoV-2 interact with various host epigenetic enzymes like histone deacetylases (HDACs) and bromodomain-containing proteins to antagonize cellular signalling. The central role of epigenetic factors in SARS-CoV-2 pathogenesis is now exploited as promising biomarkers and therapeutic targets against COVID-19. This review article highlights the ability of SARS-CoV-2 in regulating the host epigenetic landscape during infection leading to immune evasion. It also discusses the ongoing therapeutic approaches to curtail and control the viral outbreak.

1. Introduction

Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2), the causative agent of Coronavirus disease-19 (COVID-19), initially emerged in December 2019 in Wuhan, China, and since then has caused a global catastrophe by infecting millions. On March 11, 2020, WHO designated COVID-19 a pandemic after a dramatic spike in the number of cases outside China. The SARS-CoV-2 infection has emerged as one of the most significant pandemics in human history, affecting over 543 million people in 216 countries and territories and resulting in over 6.3 million deaths as of June 2022. SARS-CoV-2 belongs to the genus of the β-coronavirus under the subfamily Orthocoronavirinae and family Coronaviridae [1]. It is the seventh CoV identified to be infecting humans. The other CoVs identified are less pathogenic HCoV-HKU1, HCoV-NL63, HCoVOC43 and HCoV-229E, which cause mild upper respiratory tract infections leading to common colds and highly pathogenic middle eastern respiratory syndrome (MERS)-CoV and SARS-CoV that causes severe respiratory tract infections [2,3]. Initially, the lack of knowledge about the interaction of SARS-CoV-2 with the host significantly hampered the development of therapeutics. But the advancement in vaccine research and fast-track approval of various vaccines and administration slowed down the infection and mortality rates. Still, the emergence of resistant and more transmissible new variants has aggravated the problem manifold. Therefore understanding the biology and

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mode of infection is extremely important to generate efficient therapeutics.

SARS-CoV-2 requires continuous exploitation of host cell metabolism and transcriptional machinery to ensure successful infection. To achieve this, the viral determinants must control the host genome expression by regulating the transcription of critical genes and chromatin dynamics [4]. To do so, SARS-CoV-2 hijacks the host epigenetic mechanisms like DNA-methylation, acetylation, histone modifications etc. [4,5]. SARS-CoV-2 infection induces a plethora of changes in the host's epigenetic landscape. On one side, the infected cell activates various pathways by epigenetic changes to promote an antiviral environment. In contrast, on the other side, the virus tries to switch off essential genes causing altered cellular transcription to control antiviral responses promoting its survival and replication [1].

Epigenetic modifications are reversible post-translational changes occurring at the DNA, histone proteins and RNA level to regulate the gene expression without altering the nucleotide sequence. Therefore, a deep understanding of the host-cell chromatin dynamics involved in regulating specific genes during SARS-CoV-2-host interaction is essential. Hence, the current review attempts to showcase the effect of the host epigenetic landscape on determining SARS-CoV-2 infection outcome, which has been less explored.

2. Structure of SARS-CoV-2

The SARS-CoV-2 genome is 27–32 kb long and consists of a single-stranded positive-sense RNA of 9860 amino acids that encodes various structural and non-structural proteins [6]. The virion is an enclosed particle with a protein covering it. The single-stranded RNA genome is contained in a shell termed the capsid, which is made up of spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. Under electron microscopy, coronaviruses have a characteristic “crown” or “solar corona” appearance due to spike proteins on the capsid. The virus also encodes various non-structural proteins (Nsp) besides the above-mentioned structural proteins.

2.1. Structural proteins

2.1.1. S protein

The spike glycoproteins are integral membrane-spanning proteins composed of three identical units of the polypeptide projecting out from the viral surface [7]. It is crucial in viral evasion into the host cell, mainly targeted for developing antiviral vaccines and drugs [8]. There are two functional subunits of spike protein, namely the S1 subunit and the S2 subunit [9]. The S1 subunit consists of a receptor-binding domain responsible for the attachment of the virus to the host cell [7]. In contrast, the S2 subunit comprises a fusion peptide responsible for initiating the fusion of the virus with the host cell membrane [10].

2.1.2. E protein

Coronavirus E protein is a small, integral membrane protein of 8.4 to 12 kDa and constitutes 76–109 amino acids [11,12]. It assembles into a homopentameric cation channel, playing an essential role in viral antigenicity [13]. It consists of three parts: a hydrophilic domain of 7–12 amino acids long, a hydrophobic transmembrane domain of 25 amino acids long and a long hydrophilic carboxyl terminus [11]. This envelope protein acts as viroporin that accumulates in the host membrane, ultimately forming protein-lipid pores for ion transportation [10,11].

2.1.3. M protein

These type III transmembrane glycoproteins are coronavirus's most abundant structural protein [14]. It consists of a short protruding NH_2-terminal outside the virion and a long COOH domain in the cytoplasmic side of the virus [15]. These are 222 amino acids long and have a significant functional role in RNA packaging [10,16]. It has been a prime factor in the virus-specific humoral response [17].

2.1.4. N protein

These are types of phosphoproteins involved in packaging viral RNA with ribonucleocapsid [18].

2.2. Non-structural proteins

The ORF region encodes 16 non-structural proteins with different functions [6]. The Nsp1 protein manipulates host mRNA translation, innate anti-viral immunity and inflammatory responses, ultimately promoting viral infection and pathogenesis [19]. Nsp2 is a replicase product which proofreads viral replication and interacts with host cell prohibitin1 and prohibitin2, thereby modulating the host cell environment [10,20]. The most significant protein encoded by the genome of SARS-CoV-2 is Nsp3, with a molecular mass of 200 kDa and is crucial for its protease activity [21]. It plays an essential role in releasing active Nsp1, Nsp2 and Nsp3 by cleaving Nsp1-Nsp2, Nsp2-Nsp3 and Nsp3-Nsp4 from the viral polypeptide [22]. Nsp4 is a membrane-spanning protein containing a transmembrane domain that adheres to a viral replication-transcription complex to modify the endoplasmic reticulum membrane [10]. Nsp5 is a proteinase involved in viral polyprotein processing during replication [23]. Nsp6 is a transmembrane protein having auto phagosome formation capacity [24]. Nsp7 forms a hexadecameric super-complex with Nsp8 and Nsp12 to achieve the RNA polymerase activity of Nsp8 [25]. The Nsp8 protein has been shown to aggregate with several other Nsp's and colocalise with these Nsp's in cytoplasmic complexes that are important for viral RNA synthesis [26]. Nsp9 evolved from a protease and is a single-stranded RNA-binding viral protein involved in viral replication [27,28]. 148-amino acid-containing protein Nsp10 contains two zinc finger motifs and is found to be interacting with both Nsp14 and Nsp16 to upregulate their 3′-5′ exoribonuclease and 2′-*O*-methyltransferase activities, respectively [29,30]. The structural dynamics and functional relevance of the 13 amino acid long Nsp11 are still unknown [31]. Nsp12 is an RNA-dependent RNA polymerase responsible for viral genome replication and transcription [32,33]. SARS-CoV-2 Nsp13 has RNA helicase activity with zinc (Zn) binding domains associated with replication and transcription [34]. [10]. Nsp14 has exoribonuclease activity required for high-fidelity replication [35]. Nsp15 has Mn^{2+}-dependent ribonuclease activity, providing charge shielding to increase the favorability of the RNA-Nsp15 interaction [10,36]. Nsp16 has 2′-*O*-methyltransferase activity and plays a crucial role in host immune evasion [37].

3. SARS-CoV-2 life cycle

3.1. Virus entry

SARS-CoV-2 penetrates the host cell membrane by targeting the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of epithelial cells lining the respiratory tract (Fig. 1). The initial interaction begins with the homodimerisation of the S protein, bulging from the surface of the virus and facilitating its interaction with the ACE2 receptor; an N501T mutation in the ACE2 receptor is reported to enhance the host-virus interaction [38]. The S proteins of SARS-CoV-2 are divided into two classes, S1 and S2 [39]. The receptor-binding domain (RBD) of the surface-exposed S1 determines virus cell tropism and virulence by explicitly targeting the host cell's receptor. In contrast, the peptide fusion and the heptad repeat regions in the domain of the S2 transmembrane mediate the fusion of cellular and viral membranes after substantial rearrangements of conformation [40–42]. To mediate efficient internalization of the virus inside the host cell, proteolytic cleavage of the associated S proteins by host proteases like furin or transmembrane serine protease 2 (TMPRSS2) is necessary. Upon cleavage, the virus can either enter by membrane fusion from the outside, in which the virus's RNA genome gains entry to the cytoplasm, in which the receptor-bound virus is enclosed by the cell membrane and gains access into the cytoplasm within a vesicle or cyst [43].

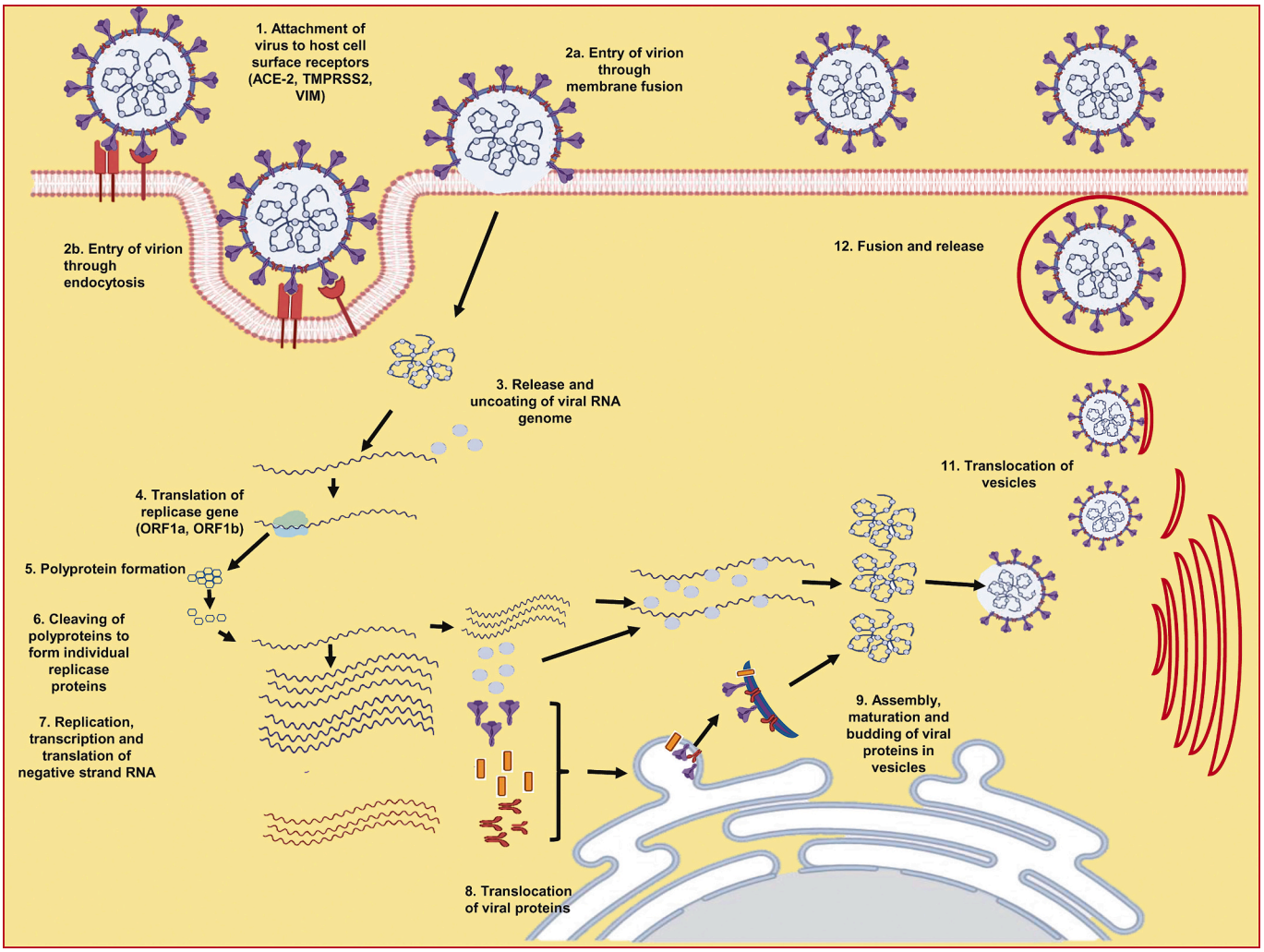

Fig. 1. The life cycle of SARS-CoV-2.

3.2. Translation of viral replication machinery

Once inside the host cell, the virus sheds its capsid and releases the viral RNA into the cytoplasm, which undergoes transcription and replication by the viral enzymes [44]. The resultant viral RNAs are mainly carried by ORF1a and ORF1ab, translated with the help of host ribosomes, forming two large polyproteins, pp1a and pp1ab, which are cleaved to generate various essential proteins [45].

3.3. Replication

For the production of full-length negative-strand RNA, replicase proteins are in charge, which is then employed as a template for the transcription of virion genomic RNA [46,47]. Unlike positive-strand RNA, mRNA is complementary to negative-strand RNA, which cannot translate directly, so it is first transcribed to positive-strand RNA with the help of RNA polymerase [39]. To produce shorter mRNAs, the full-length negative-strand RNA is translated. These shorter mRNAs encode structural proteins during translation, such as N, M, E, S and other non-structural auxiliary proteins, such as viral proteinases [45].

3.4. Translation of viral structure proteins and virion assembly

In a region between the endoplasmic reticulum (ER) and the Golgi apparatus, newly generated positive-strand viral genomic RNA and proteins for non-structural and structural parts are transported to the assembly sites [48]. The ER and the Golgi apparatus are responsible for protein synthesis, post-translational modification of the protein, wrapping it into membrane-bound vesicles, and trafficking those vesicles. All the nascent virions assemble, mature, and eventually bud out in the Golgi membranes as vesicles [49].

3.5. Release of virus

These vesicles are conveyed to the host cell membrane, where they bind and are released into the extracellular environment by exocytosis. Exocytosis is the mechanism by which fully formed virions are discharged from the host cell and are primed to bind to other host cells. [50,51].

4. Epigenetics

Epigenetics studies intricate interactions between the environment and the host genome that alters gene expression without modifying the DNA sequence. Epigenetic changes or “tags” such as DNA methylation and histone modifications change DNA accessibility and chromatin structure, affecting gene expression patterns (Fig. 2) [52].

4.1. DNA methylation

The primary epigenetic marker seen in DNA is the methyl group addition to the C5 site of cytosine residue covalently catalyzed by DNA

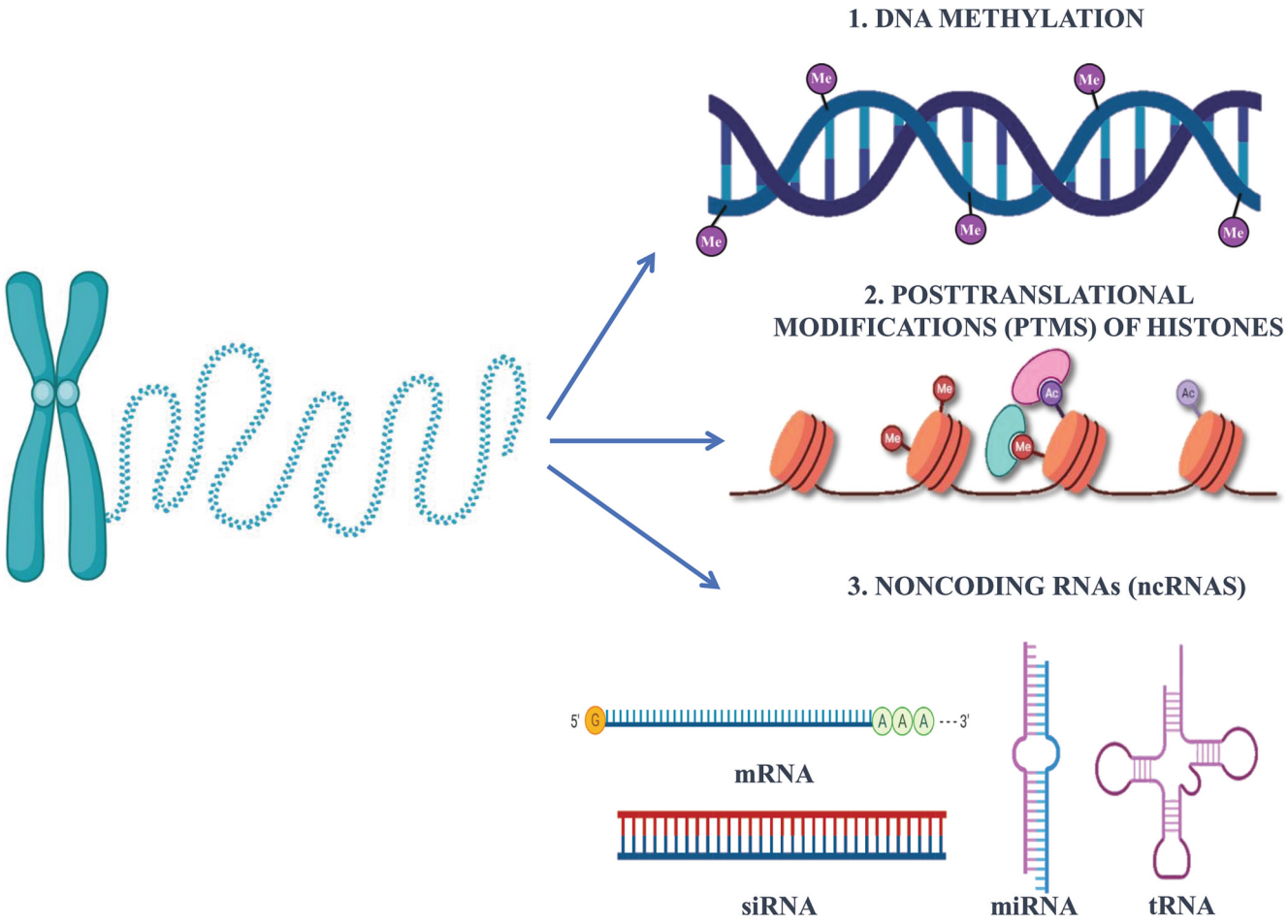

Fig. 2. Three significant epigenetic mechanisms affecting the gene expression patterns i) DNA methylation, ii) Post-translational modification of histones and iii) Non-coding RNAs.

methyltransferases (DNMTs) which results in 5-methylcytosine [53]. This alteration is more common in CpG dinucleotide-containing areas and is frequently found in regulatory regions that restrict gene expression. CpG methylation is required for transposon and transcriptional element suppression, genomic imprinting, X-chromosome inactivation, and tissue-specific gene expression throughout differentiation and development [53,54]. The distribution of CpG methylation alters predictably during development. Methylation is eliminated across the genome during early development and then reintroduced in all but CpG regions. Until later in development, when some of the CpG islands become methylated, they remain hypomethylated [55,56]. In embryonic stem cells and fetal fibroblast cells, one-third of cytosine methylation is also found outside CpG islands and is critical for regulating gene expression [57].

A methylated cytosine can restrict transcription by blocking transcription factor binding or increasing the binding of other transcriptional repressors. DNA methyltransferases (DNMTs) aid the de novo methyltransferases DNMT3a, DNMT3b, and DNMT1 in detecting the non-methylated daughter strand methylating it at CpG dinucleotides during DNA replication [58]. Base-pairing principles allow reciprocal methylation to be maintained across consecutive DNA replication cycles, providing a means for relocating a nongenetic characteristic from one cell to another, making methylation a persistent and stable epigenetic criterion [59]. A methylation pattern is necessary for development, whereas abnormal DNA methylation leads to tumours' growth. DNMT1 is reported to interact with various cell cycles proteins like PCNA, p53, EZH2 and HP1 to regulate cell cycle and apoptosis, whose activity is controlled by Ras family GTPase as uncontrolled activity of DNMT1 induces cancer [60,61]. Similarly, methylation of the *FAS* gene is shown to activate the Ras-Raf-MEK-ERK-Elk pathway, leading to cancer development. Besides methylation, the removal of –CH3 group from the methylated cytosine, called DNA demethylation, is also responsible for the activation of genes [62].

4.2. *Post-translational modification of histones*

Histones undergo various post-translational alterations, such as acetylation, ubiquitination, phosphorylation, and methylation, that alter chromatin structure and affect gene expression [63,64]. As per the "histone code" idea, several kinds and amalgamations of modifications affect the structure of chromatin and its transcriptional potential in different ways [65]. The most well-studied histone modification that promotes transcription is the acetylation of histones H3 and H4, which have lysine residues at the amino group in their amino-terminal. The transcriptional co-factors like p300 and cAMP response element-binding protein catalyse histone acetylation by attaching histone acetyltransferases to the acetylation regions [66]. The CpG methylation and inactive chromatin conformation are linked to histone deacetylation. Deacetylation is catalyzed by four types of HDACs, each controlled by some modification that occurs post-translationally [67,68]. Histone acetylation can be reversed with several histone lysine methyltransferases and demethylases targeting particular lysines and mono-, di-, or trimethylation states [69–71]. Histone methylation is regulated through the enzyme histone methyltransferase (HMTs) and histone demethylase (HDMs). Histone lysine methylation is a significant histone modification that affects gene expression, albeit the factors of expression

are complicated and rely on the location of the lysine and the level of its methylation. The H3K4 methylation is associated with the activation of genes to regulate the normal regulatory circuits for development [72].

4.3. Non-coding RNAs

Long non-coding RNAs (lncRNAs) partly silence genes by attracting remodelling complexes that induce histone methylation, such as the polycomb complex [73]. LncRNAs can attract RNA-binding proteins (RBD), which prevent histone deacetylation or transcription factors from binding to promoter areas [74]. These multi-parametric approaches make long non-coding RNAs crucial for X-chromosome inactivation and imprinting [75]. Small inhibitory RNAs (siRNA) and dicer-dependent microRNAs (miRNA) have been demonstrated to suppress transcription through various procedures, like employing particular argonaute proteins to establish epigenetic remodelling complexes to enhance histone deacetylation, histone methylation, and DNA methylation [76,77]. Protein interaction world-interacting RNAs (21–30 nt) are single-stranded subparts of short non-coding RNAs that have also been demonstrated to function in RNA-induced epigenetic silencing transgenerational inheritance [78].

5. Regulation of host epigenetic mechanisms by SARS-CoV-2 to enhance viral replication and disease severity

All viruses have employed epigenetic processes, particularly CpG methylation, for centuries to cause syncytium development and enterocytosis. Despite minor distinctions between DNA and RNA viruses, viruses exploit host epigenetic reprogramming to evade host immune responses. Different processes like molecular and epigenetics that govern coronavirus pathogenesis are complicated and mainly rely on the host-virus interactions that guide the entry of virions, viral replication, and immunopathogenesis. SARS-CoV-2 is similar to other coronaviruses as it can manipulate the host's innate immune system [79]. SARS-CoV-2 relies heavily on epigenetic processes to gain entry into the host, resulting in the severe sickness and mortality seen frequently during the COVID-19 pandemic.

Epigenetic processes can activate and inactivate genes, discover the transcription of proteins at a particular point in time, and have a crucial function in governing the basal operations of the cell. Diverse cells, tissues and organs have a specific set of genes switched on or off depending on their requirements. Epigenetic silencing is a well-known approach for turning genes off, resulting in unequal expression. Epigenetic silencing means that genomic alterations that do not affect the host's sequence can be reverted in certain conditions. Three processes work together to quiet genes in these various cells that perform different functions: DNA methylation, modifications of histones, and RNA-mediated silencing [80,81]. The above three are functional and crucial regulators that alter gene and arbeit expression flexibly and seamlessly.

5.1. Regulation of DNA methylation

DNA methylation regulates the host expression patterns during viral infection, which is implicated via the virus to replicate its genetic material for proliferation. Corley et al. have shown that DNA methylation is dependent on the age group as the methylation in adults is higher compared to children resulting in more infection in adults [82]. The above can be related to the human immune system as the dendritic cells and macrophages are essential for antigen presentation over the surface of these immune cells via the toll-like receptors (TLRs). In mice, it has been reported that defects in TLR raise the risk of pneumonia with inflammation suggesting this could be the reason for the severity of COVID-19 in adults. Upon activation of TLR, the different temporal and spatial response occurs by cell-to-cell interaction or interferon secretion for managing the immunological memory to clear the pathogen by the host's antiviral response. To overcome this phenomenon, viruses downregulate the interferon production by the host by modulating their genes. It has been found that de novo methylation of the INF-γ promoter silence the interferon-stimulated genes (ISGs) and blocks the antiviral response in the host. Post-transcriptional modification of RNA by N6-methyladenosine, also known as m6A methylation [83]. DNA methylation has recently been associated with the ACE2 gene regulation, suggesting that the SARS-CoV-2 infection may be influenced by the host epigenome (Fig. 3).

Furthermore, Age-dependent DNA methylation was observed in airway epithelial cells near the ACE2 gene's transcription initiation point. Researchers utilise data from different samples of various biological ages Illumina DNA methylation arrays to discover one that is CpG (cg085599149) at the transcription start point of ACE2 showed reduced methylation levels as people aged [84]. Different epigenetic mechanisms have been associated with the expression of the ACE2 gene in various body parts, as mentioned in Fig. 3 [85–91].

Patients with multiple diseases and increased ACE2 expression in their lungs are highly prone to severe COVID-19 disease. Structural experimentation and thorough investigations discovered many crucial regulators of ACE2 in the lungs of humans. It includes genes deciphering for the epigenetics enzyme such as histone deacetylase 2 (HDAC2), histone acetyltransferase 1 (HAT1), and lysine demethylase 5B (KDM5B), along with specific histone acetylation (H3K27ac), and histone methylation (H3K4me1 and H3K4me3) marks. ACE2 is found to be positively regulated by the genes mentioned above. Moreover, regulation of KDM5B to the accessibility of chromatin is made by eliminating active chromatin signals like di- and trimethylation from histone H3's lysine 4 (H3K4), which is essential for the transcription of the gene and DNA repair. Overexpression of ACE2 and disease severity are driven by epigenetic regulation of the lung gene. Furthermore, it was discovered that inhibiting KDM5B in breast cancer cells causes an interferon reaction, which leads to the resilience of DNA and RNA viral infection, implying that KDM5B could be a possible goal for eradicating COVID-19 [85].

5.2. Regulation of histone condensation

In humans, chromatin changes like histone lysine methylation and histone lysine acetylation control the expression of the ACE2 receptor [84]. Sirtuin 1 (SIRT1), a NAD-dependent histone deacetylase, is also shown to influence ACE2 expression during stressful situations. As a result, epigenetic regulators are essential in human tissue to express the ACE2 receptor. A recent global study of COVID-19 patients and healthy control individuals' blood samples revealed that histone epigenetic modifications play a crucial role in the modulation of ACE2 gene expression. In COVID-19 patients, increased ACE2 expression has been linked to histone modifiers such as KDAC2, KAT1, and histone demethylase [85–91].

5.3. Histone citrullination

Histone citrullination is an epigenetic post-translational modification that changes the structure of chromatin in histone by converting arginine to citrulline. Citrullination, also known as deimination, is a histone modification that results in a looser chromatin structure and a reduction in hydrogen bonds. Citrullination of histone H3 has been found to free up chromatin and enhance gene transcription, for example. The peptidyl arginine deiminases (PADs) family of enzymes, including PAD1, PAD2, PAD3, PAD4, and PAD6, catalyses this epigenetic process [92,93]. PAD4, also known as PADI4, has been found to have a critical function in modulating chromatin decondensation and gene regulation [94].

Furthermore, PAD4-mediated citrullination of histones H3 and H4 has been linked to cell death and inflammatory pathways [7,95,96]. This epigenetic mechanism is associated with the pathophysiology of inflammatory diseases, including rheumatoid arthritis and cancer.

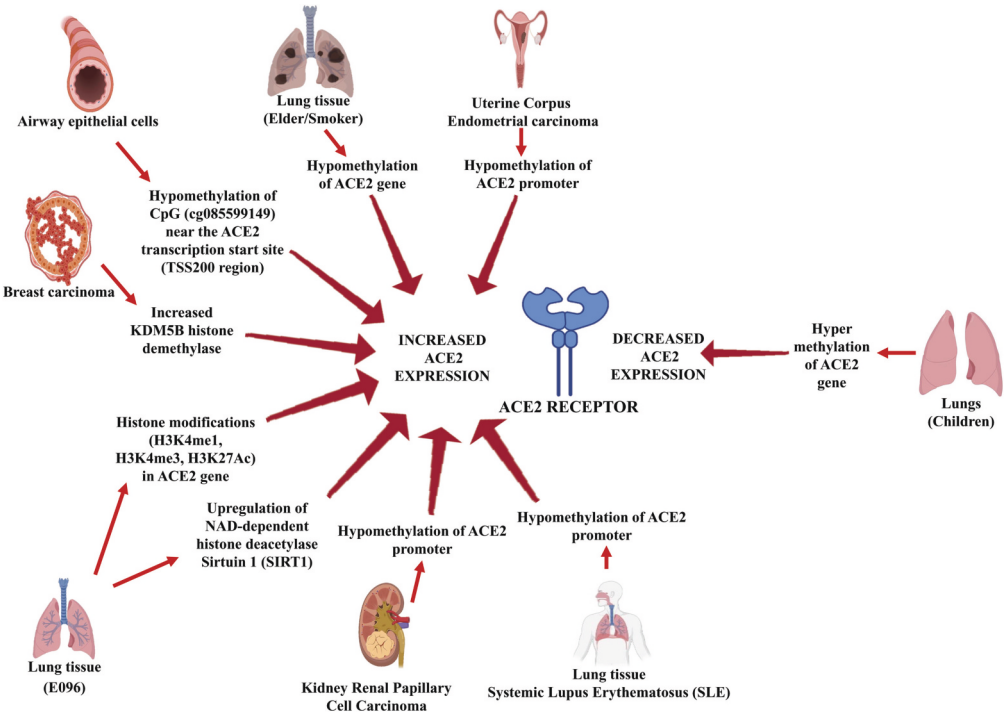

Fig. 3. Schematic illustration of the epigenetic regulation of ACE2 gene expression in different body parts.

Researchers are still learning more about the intricate roles it plays in cellular processes. The creation of neutrophil extracellular traps (NETs) is linked to the severity of COVID-19 [97]. Cytotoxic extracellular histones are released during NET formation, and their presence has been associated with the onset and progression of various acute inflammatory disorders [98]. Extracellularly present histone H3 and numerous other damage-associated molecular patterns (DAMPs) and neutrophil-related molecules were found in the plasma of 117 COVID-19-positive ICU patients and their evolution. When COVID-19-positive patients were admitted to the ICU, histone H3, MPO, and DNA-MPO complex levels were all convincingly higher than in control samples [98,99].

However, after 4+ days, the levels of all individual markers remained elevated in a subgroup of 54 patients in contrast to admission. Histone H3 was identified in 28 % of ICU patients upon admission and 50 % after their stay. Notably, scientists found histone proteolysis in the plasma of 47 % of histone-positive patients. Histone H3 was linked to thromboembolic events and secondary infection during ICU stays [100,101]. In contrast, non-cleaved histone H3 was linked to the desire for vasoactive therapy, invasive ventilation, and the development of acute renal injury [102]. Their findings back up the efficacy of medications aimed at reducing NET formation. They also show that more targeted therapies aimed at histone neutralisation should be evaluated as a therapy choice for COVID-19 patients with severe disease [99].

6. Host immunity and disease severity

In severe and critical COVID-19 patients, SARS-CoV-2 has been demonstrated to alter normal immunological responses, resulting in a weakened immune system and uncontrolled inflammatory reactions [103]. Lymphocytic activation and dysfunction, granulocyte and monocyte abnormalities increased cytokine production, and elevated antibodies are various immunological characteristics associated with COVID-19. Lymphopenia is a common symptom of COVID-19 patients, especially in difficult situations [104–106]. Patients' CD4+ and CD8+ T cells have high levels of CD69, CD38, and CD44, and virus-specific T cells from severe cases have a central memory phenotype with increased levels of IFN-γ, TNF-α, and IL-2 [107–109]. The increase of T cell immunoglobulin domain, killer cell lectin-like receptor subfamily C member 1 (NKG2A), programmed cell death protein-1 (PD1), and mucin domain-3 (TIM3) in lymphocytes, nevertheless, leads to a phenotype of exhaustion. The percentage of eosinophils, basophils, and monocytes is reduced in severe cases, but neutrophil levels are much elevated. A critical feature of chronic COVID-19 is increased cytokine production, specifically IL-1, IL-6, and IL-10 [110,111]. Furthermore, the total antibody titer and IgG levels have increased [110,111].

7. Role of non-coding RNAs in SARS-CoV-2 infection

The eukaryotes' genome comprises non-coding RNAs that are not transcribed into proteins and have regulatory and housekeeping functions. Based on their size, regulatory non-coding RNAs are broadly divided into lncRNA and short non-coding RNAs, including siRNA, PIWI-interacting RNA (piRNA), and miRNA. miRNAs are 22 nucleotide long-short RNA molecules that post-transcriptionally regulate gene expression [112]. MiRNAs are also reported to epigenetically regulate innate and adaptive immune responses during bacterial and viral infections [112–114]. Therefore SARS-CoV-2 hijacks this machinery by explicitly targeting the host proteins that might function as the regulators of viral replication and avoiding host repression [115,116]. The virus solely depends on the host cellular machinery of RNA polymerases, ribonucleases and endonucleases for the biogenesis of viral miRNA [117]. These viral miRNAs are reported to target significant pathways involved in immune responses like MAPK signalling, T cell activation, vascular endothelial growth factor signalling, fibroblast growth factor signalling, JAK and STAT signalling etc., leading to the successful establishment of infection [5].

Lai et al. have shown that viral miRNAs often mimic crucial host miRNAs to disrupt the host immune response against the virus without being detected by the host immune system [118]. SARS-CoV-2 is reported to release its viral-miRNA inside the host cell that can hijack primary anti-viral mechanisms like apoptosis, autophagy, generation of anti-viral proteins and production of various cytokines. Viral miRNAs are also known to inhibit transcription by targeting the association between RNA polymerase II or other transcription regulators to the host

gene promoters. SARS-CoV-2 miRNAs can also interact with host miRNAs to regulate host defence mechanisms like stimulating pro-inflammatory cytokines and Ca^{2+} signalling [119]. Viral miRNA 1468-5p, 1307-3p, 3954-3p, 3691–3p, 3611, 5197, and 8066 are predicted to regulate the innate and adaptive immune responses upon SARS-CoV-2 infection by viral epigenetic sensory mechanism [120–122]. These viral miRNAs successfully escape the host immune surveillance by suppressing various mRNA deadenylase transcription complexes like CNot10 subunits, CNot6 ligands and carbon catabolite repression [123].

The abnormal host miRNA expression due to SARS-CoV-2 infection is mainly associated with dampening immune responses. Various reports have suggested the use of host miRNA by SARS-CoV-2 as a novel immune evasion method, but the precise mechanisms by which host miRNA affects the epigenetic interactions with the host are yet to be elucidated. Pontecorvi et al. have reported that various host-miRNAs regulate the expression of essential proteins required for SARS-CoV-2 cell invasions like furin, ADAM17, TMPRSS2 and ACE2 [124]. ACE2 expression is strictly regulated by hsa-miR-143, hsa-miR-421, hsa-miR-27b-3p and hsa-miR-9-5p whereas hsa-miR-106a, hsa-miR-19 and hsa-miR-20 regulate the expression of furin [124–126]. Hsa-miR-3849-3p and hsa-miR-145 regulate the expression of TMPRSS2 and ADAM17, respectively [124,127]. During viral infections, various host miRNAs function as a double-edged sword as they favour both host immune defence mechanisms and viral pathogenesis. They are reported to target viral mRNAs involved in viral genome replication or translation to inhibit SARS-CoV-2 pathogenicity or stabilise viral RNA, rendering it resistant to host immune response [128]. An in silico study by Srivastava et al. has identified nearly 873 human miRNAs involved in modulating innate and adaptive immune responses against SARS-CoV-2 infection [129]. Lai et al. have shown that the binding of OC43, the coronavirus nucleocapsid protein, to hsa-miR-9 regulates innate signalling by activating NF-κB [118]. It is reported that hsa-miR-323a-5p, hsa-miR-17-5p, and hsa-miR-20b-5p largely targeted viral ORF1ab and S regions in their anti-COVID-19 activities. Whereas hsa-miR-3934-3p, hsa-miR-5197-3p, hsa-miR-8066 and hsa-miR-98-5p are reported to regulate the production of viral S protein [123,130].

Other non-coding RNAs like lncRNA are also pivotal in establishing SARS-CoV-2 infection by regulating various cellular processes. The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA and nuclear paraspeckle assembly transcript 1 (NEAT1) lncRNA are reportedly involved in inflammasome activation in COVID-19 infected cells and can be used as biomarkers to monitor disease severity [131,132]. Recently Qu et al. have found that MALAT1 lncRNA enhances viral transcription by reducing the epigenetic silencing and regulating the interactions of promoter and enhancer [133]. Similarly, NEAT1 lncRNA is shown to form nonmembranous organelle nuclear paraspeckles to control RNA regulatory processes [134]. Moreover, the higher pathogenicity rate of SARS-CoV-2 is also predicted due to variability in viral non-coding RNA and their fast mutation rates.

8. Effect of SARS-CoV-2 virulent proteins in modulating the host epigenetics landscape to regulate immune defence mechanisms

SARS-CoV-2 has the largest genome among all known coronaviruses that encode many structural and non-structural proteins essential in delaying pathogen recognition and controlling various antiviral responses. A recent study by Gordon et al. tried to map the viral protein components with their host interacting partners [135]. They found around 332 human proteins interacting with their viral components, of which 8 are related to epigenetics machinery [135]. Similarly, Albarrán et al. have also analysed multiple transcriptomes obtained from SARS-CoV-2 infected cell lines, characterised different pathways enriched with transcription factors relevant for SARS-CoV-2 infection, and identified more than 60 proteins involved in epigenetics machinery during SARS-CoV-2 infection having therapeutic potential [4].

Nsp5, a protease encoded by SARS-CoV-2, interacts with histone deacetylase 2 (HDAC2), hindering the production of interferons and inflammation [44]. HDACs are extremely necessary to control gene expression as they mainly act as transcriptional suppressors by removing histone acetylations, and HDAC2 is explicitly responsible for stimulating various interferon-specific genes (ISG) through BRD4 for an effective antiviral response [136]. It is predicted that Nsp2 cleaves the nuclear localisation signal of HDAC2, suppressing its translocation to the nucleus and leading to the inhibition of various antiviral responses [137]. Nsp5 is also predicted to cleave the nuclear localisation signal of tRNA methyltransferase 1 (TRMT1), inhibiting its transport to the nucleus and localising it in mitochondria [136]. Josling et al. have shown that the C terminal end of the viral envelope protein E mimics the N-terminal tail of histone H3 and competitively binds to bromodomain proteins BRD2/4 instead of histone H3 disrupting the downstream transcriptional activities. BRD2/4 recognise acetylated histones and activates transcription [138].

SARS-CoV-2 encodes ion channel proteins like ORF8a and ORF3a, collectively called viroporins. These hydrophobic proteins are reported to activate the NLRP3 inflammasome, triggering a cytokine storm leading to tissue inflammation, damage and respiratory illness [5]. Similarly, another protein encoded by the virus open reading frame 3b (ORF3b) is also known to regulate the production of type I interferons. The SARS-CoV-2-ORF3b encodes a 22 amino acids long protein due to the presence of a premature stop codon and is considerably shorter than its ortholog, SARS-CoV, which is 154 amino acids long [5]. The presence of a shorter variant of ORF3b in SARS-CoV-2 is attributed to its increased virulence. Konno et al. have shown that inserting a premature stop codon in the coding sequence of SARS-CoV-ORF3b made the virus much more effective in inhibiting type I interferon response compared to wild-type SARS-CoV-ORF3b [139]. It is predicted that ORF3b can effectively inhibit various host defence mechanisms early in the infection cycle by inhibiting interferon production by an epigenetic mechanism before activating B and T cells [5].

Further, viral proteins like ORF10 and Nsp13 are reported to interact with the human Cullin-RING E3 ubiquitin ligase complex and ubiquitin-specific peptidase 13 (USP13), respectively [44,115]. Since these complexes ubiquitinate protein for degradation, it is predicted that SARS-CoV-2 hijacks the protein degradation mechanism inducing the proteasomal degradation of host restriction enzymes and promoting viral replication. Nsp13 is also hypothesised to regulate IFN signalling and NF-κB-mediated inflammatory responses by interacting with TLE, TBK1 and CENPF [5]. ORF8 and Nsp8 are predicted to interact with DNMT1 and MEPCE, respectively [44]. The interaction of ORF8 with DNMT1 is unique as it has long-term effects even after recovering from the disease. DNMT1 maintains physiological DNA methylation patterns and is involved in replication machinery during mitosis to maintain the same epigenetic pattern in daughter cells [140]. Dysregulation in DNMT1 activity during COVID-19 is predicted to cause atherosclerosis, liver dysfunction and diabetes [140]. Similarly, MEPCE is an essential regulator of RNA Pol II-mediated transcription elongation and its dysregulation influences the transcriptional regulation of the virus [141].

9. Regulation of cytokine storm

Host antiviral immune response includes activating the inflammasome complex that is strictly regulated. But SARS-CoV-2 infection is characterised by a dysregulated immune response leading to abnormal secretion of various pro-inflammatory cytokines causing acute inflammation and tissue damage, termed as ‘cytokine storm’. The elevated levels of different pro-inflammatory cytokines like IL-1β, IL8, TNF-α, IFN-γ, IL-12, IL-18, IL-33, IL-6, IL-4, monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1-α (MIP1A) and granulocyte-colony stimulating factor (G-CSF) cause an excessive influx of various immune cells to the site of infection, leading to lungs damage and multi-organ failure [142–144]. The cytokine storm is a familiar principal mechanism of acute respiratory distress syndrome (ARDS),

which is the chief cause of death upon SARS-CoV-2 infection [145]. Generally, ARDS makes immunocompromised, chronically ill, and older patients more susceptible to hyperinflammation [146].

The initiation of ARDS involves histone modifications that regulate the expression of genes associated with immune response during SARS-CoV-2 infection [128]. The pattern recognition receptors in macrophages and dendritic cells recognise the pathogen-associated molecular patterns leading to their activation and initiation of a specific, robust and rapid cascade of downstream signalling to generate an effective immune response against the invading virus [147]. It is widely reported that TNF and IFNs are the primary cytokines that elicit the antiviral response [44,148]. So their promotors are strictly regulated by histone modifications for quick response to external stimuli. Therefore, epigenetic mechanisms are responsible for guaranteeing a functional and highly regulated host response beyond the initial activation wave.

Several innate immune signalling pathways involving TLR3, TLR4, STAT1 and MyD88 are activated during viral infections to control the severity of infection. Activation of these pathways promotes an antiviral environment in the host leading to instant secretion of cytokines like type I interferons and TNFα to diminish the infection in vivo and in vitro [44,149]. The production of these cytokines is under strict epigenetic regulation as the promoters of these cytokines are marked by H3K4me3, H3K27me3 and H3K9me2, which are involved in the regulation of cytokine production [148]. The presence of H3K9me2 prevents histone tail acetylation and promotes DNA methylation and formation of heterochromatin instead of euchromatin by the recruitment of transcription repressor heterochromatin protein 1 (HP1) family, whereas H3K4me3 is a transcription activating histone modification and regulates various TLRs [149]. Demethylation of IFN-regulated genes, NF-κB, and essential cytokine genes favour the expression of pro-inflammatory cytokines and chemokines, thus increasing cytokine storm incidence [148].

Similarly, the promoter region of IL-6 is regulated by DNA methylation. So, minimising IL-6 plasma concentrations and controlling the ACE2 gene epigenetically might be a target for prevention and therapy for COVID-19 infection [148]. The activation of host epigenetic machinery strictly depends on the type of viral infection. It was observed that during SARS-CoV-2 infection, the promoters of ISG were marked with H3K4me3, the transcription-activating modification, rather than H3K27me3 [150]. But upon infection of Calu3 cells with MERS-CoV, the promoter sites were mainly marked with HEK27me3 instead of H3K4me3, leading to a diminished transcription of ISG genes [81,151]. Altogether, the hyperinflammatory cytokine and chemokine storm observed in ARDS patients result from epigenetic modifications in both SARS-CoV-2 infected epithelial cells and immune cells in their vicinity.

10. Epigenetic regulation of immunocompetence related genes during coronavirus infection

SARS-CoV and SARS-CoV-2 share 79.6 % of genomic similarity and use ACE2 receptors for their internalization; therefore, their pathophysiology closely resembles each other [152]. Both of them cause hyper-inflammation in the airways leading to their damage. Under normal conditions, the virus specific-T cells are recruited to the site of infection upon initial inflammation to clear the infected cells and minimize damage, but coronaviruses initiate a dysfunctional immune response that leads to the overproduction of pro-inflammatory cytokines and imbalance of T cells, causing acute respiratory disease syndrome and multi-organ damage [153]. The human leukocyte antigens (HLA) gene complexes act as a defence mechanism against viruses. HLA proteins are encoded by the MHC genes in humans, showing high polymorphism and affecting cells responses to pathogens [154]. In silico data suggest that the *HLA-B*46:01* allele enhances the severity of SARS-Cov-2 infection and is identified as a vulnerability biomarker. At the same time, the *HLA-B*15:03* allele reportedly protects SARS-CoV-2 from host immune response [155]. Whereas *HLA-B*07:03*, *HLA-B*08:01* and *HLA-B*46:01* are associated with susceptibility and resistance against SARS-CoV [152]. Another set of proteins, defensins (α, β, and θ defensins) rich in cysteine, are reported to act against bacteria, fungi and viruses as the first line of defence. In the SARS-CoV-2 positive patients', some of the β-defensin genes *DEFB4A*, *107B*, *106B*, *4B*, *103A* and α-defensin gene *DEFA1B* are significantly downregulated. Idris et al. have suggested that the downregulation of these genes provides compromised innate immunity during SARS-CoV-2 infection and facilitates the progression of the disease [156].

SARS-CoV infection leads to the accumulation of H3K4me1 and depletion of H3K27me3. H3K4me1 enhances the transcription of genes required for replication of SARS-CoV, but during MERS-CoV infection, a reverse phenomenon is seen, as there is more accumulation of H3K27me3 and depletion of H3K4me1 [152,157]. MERS-CoV and SARS-CoV infection are reportedly triggered by $TMPRSS_2$, which is also responsible for SARS-CoV2 infection by proteolytic cleavage of ACE2 for the entry of the virus. $TMPRSS_2$, co-expressed with ACE2, regulates its downstream signalling, including hepatocyte growth factor and protease-activated receptor-2/F2RL1 associated with enhancing prostate cancer metastasis [158,159]. Genetic variation in $TMPRSS_2$ like polymorphisms at $RS_{7364083}$ and $RS_{2070788}$ influence SARS-CoV-2 clearance [160,161]. Since ISG response plays a prominent role in controlling viral infection. MERS-CoV and SARS-CoV-2 infection are reported to significantly delay the expression and release of ISG by inhibiting the removal of repressive histone mark H3K27me3 and removing the active histone mark H3K4me3 resulting in more condensed chromatin that prevents attachment of various transcription factors [157]. The findings of the genome-wide DNA methylation array and chip methylation pipelines investigation show that the DNA methylation levels of the ACE2 gene vary depending on the tissue subtype [157]. Lung epithelial cells had the lowest levels of ACE2 gene methylation over three CpG sites (cg04013915, cg08559914, and cg03536816) relative to other tissues [162]. It is predicted that during COVID-19 infection, SIRT1 may be a target for epigenetic therapeutics due to its involvement as an NAD^+-dependent histone deacetylase in activating ACE2 activity by enhancing the ACE2 promoter during energy deprivation [163]. Furthermore, a pathway enrichment analysis suggested that KDM5B may be involved in controlling the expression of multiple genes linked to ACE2 through the acetylation and methylation of epigenetic markers such as H3K4me1, H3K4me3 and H3K27ac [87].

Cellular functions like DNA repair, replication, p53, STAT3, HIF-1α, and p65 are regulated by the acetylation and deacetylation by HDAC. HDAC in macrophages shows a pro-inflammatory response by increasing the level of TNF-α, IL-1α, IL-1β, MCP-1 and IFN-γ. HDAC2 alters the monocyte and macrophage function by inhibiting the activity of NF-κB and plays a significant role in the immune evasion strategy of SARS-CoV-2. The nuclear localization of HDAC5 induces the activation of TNF-α and MCP-1, initiating an inflammatory response [164,165]. However, a potential method to manage the inflammatory response linked to COVID-19 may involve medicines that might activate HDAC2 and enhance the nuclear export of HDAC5 [157].

11. Role of vitamins and minerals in regulating epigenetic landscape to control SARS-CoV-2 infection

Many studies have reported that many vitamins and minerals can control SARS-CoV-2 infection by regulating the epigenetic landscape through phosphorylation, acetylation, citrullination and methylation to enhance the immune response and control inflammation [166–169]. Several reports have suggested that vitamin D deficiency is associated with increased severity of COVID-19 [167,170]. In similar studies, it has been observed that SARS-CoV-2 infection outbreaks generally occur during cold winter time when the serum concentration of calcifediol/25-hydroxyvitamin D is the lowest [171,172]. The positive effect of vitamin D replacement therapy in reducing disease severity has been observed in various clinical settings. It is reported that using quercetin and vitamin D can reduce SARS-CoV-2 infection intensity by inhibiting the expression

of ACE2 on the cell surface [167,170,173]. Since vitamin D is also responsible for epigenetically controlling the signalling pathways of various pro-inflammatory cytokines, it can significantly reduce the effect of cytokine storms in COVID-19 patients [170,174]. Vitamin D is also reported to upregulate the expression of hsa-miR-145, which regulates the expression of ADAM17, which SARS-CoV-2 requires for cell invasion [175]. Therefore vitamin D deficiency can substantially affect the infection outcome.

Vitamin C acts as an antioxidant to protect macrophages and biomolecules by scavenging reactive oxygen species (ROS), thereby helping the host combat infections [174]. Various reports have suggested that vitamin C can control the symptoms of ARDS by attenuating the activation of NF-κB, which otherwise would have caused unrestricted production of pro-inflammatory cytokines, increased oxidative stress, septic shock and thick mucus formation [176,177]. Since mostly COVID-19 infection results in ARDS, there is a high possibility of vitamin C reducing the severity of SARS-CoV-2 infection. It is also reported to regulate the production of TNF-α by histone methylation [146,178]. Other vitamins, such as members of the vitamin B complex, act as co-factors for the optimal activity of DNMT in gene silencing by histone deacetylation and DNA methylation [166]. Because of the known epigenetic altering activities of vitamins, high doses of the vitamin are currently undergoing clinical trials for SARS-CoV-2.

Besides vitamins, many minerals also play a crucial role in regulating the epigenome of specific genes involved in SARS-CoV-2 pathogenesis. Minerals such as magnesium (Mg), iron (Fe), potassium (K) and zinc (Zn) have been known for a long to have anti-inflammatory, anti-viral and antioxidant activities, and their deficiency causes demethylation of IL-6 promoter and cellular damage by activation of immune cells [145]. Recent clinical studies observed that low plasma levels of minerals like Zn correlated with increased virulence and complications in SARS-CoV-2 infection in patients [179,180]. In another similar study, low levels of Zn and Mg in serum plasma were directly proportional to disease severity in SARS-CoV-2 infected patients [181]. Zn is a crucial element involved as a co-factor in many epigenetic, immunomodulatory and antioxidant pathways. Therefore the disease severity in COVID-19 patients having low plasma Zn concentrations could be due to the reduced activity of Zn-dependent histone-modifying enzymes [145]. It has also been predicted that the decreased plasma level of Zn and Mg could be due to excessive consumption of these minerals by the metal-binding pro-inflammatory cytokines that are released in large amounts during infection [182].

12. Epigenetic-based treatments for COVID-19 (combinational therapy)

Currently, no particular antiviral medications are available for SARS-CoV-2 disease, and antibiotics and vaccines are still being developed. Despite this, numerous prospective medicative procedures are being studied, and additional study is urgently required to produce effective vaccines and safe medications for treating SARS-CoV-2 infection so that both before and after exposure treatments against the virus can be developed. Even though the primitive priority would be to formulate SARS-CoV-2-based vaccines with conserved epitopes capable of eliciting neutralising antibodies or virus-specific T-cell responses, but is also equally important to identify and develop secure and potent medications to prevent SARS-CoV-2 passage of entry and replication. Given the importance of epigenetic processes in the management of various elements of SARS-CoV-2, it is no surprise that enzymes involved in epigenetic processes are being researched as remedial targets. Two clinical trials focusing on epigenetic processes have already begun. Many more clinical trials to treat COVID-19 are now underway.

Currently, studies are being carried out to identify biomarkers to know if smokers are at considerable risk of SARS-CoV-2 infection-related morbidity and mortality by checking the profiles of immune cells like T-cell and B-cell and patterns of transcription and DNA methylation [183]. Since various studies have found that histone modifications and DNA methylation modulate ACE2 expression, enzymes controlling the epigenetic changes like KDM5B, HDAC2, HAT1 and DNMT1 can be potential targets to prevent infection [184]. Therefore, the available inhibitors for these enzymes can be repurposed against COVID-19. Since SARS-CoV-2 exploits the host-epigenetic landscape, FDA-approved epigenetic drugs developed for cancer therapies can be repurposed to treat COVID-19 [148,185]. A significant culprit behind COVID-19 high mortality rates is the unregulated inflammation caused by the uncontrolled production of pro-inflammatory cytokines. Therefore drugs like Decitabine, an inhibitor of DNMT, widely used to inhibit DNA methylation in macrophages suppressing IFN response and inflammation, can be used against SARS-CoV-2 infection [148].

Polycomb repressive complex 2 (PRC2), which regulates transcription regulation through H3K27me3 enhancement at specific IFN-stimulated genes, can also be a target. PRC2 inhibitors are now being tested in newfangled cancer clinical trials and could be effortlessly repurposed to cure SARS-CoV-2 patients [186]. Interestingly, recent research suggests that vitamins and natural items can improve immunity and reduce inflammation in COVID-19 patients by acting as epigenetic modifiers [166,167,187]. Vitamin D and quercetin, for example, could be beneficial in reducing the severity of SARS-Cov-2 by decreasing ACE2 production and its putative function in regulating the cytokine storm linked to morbidity in SARS-CoV-2 sufferers [167,170]. Other methods involving epigenetic mechanisms that should be researched for treating SARS-CoV-2 infections and diseases are RNA-based therapeutics [188,189]. Novel techniques involving small interfering RNAs (siRNAs), microRNAs (miRNAs), and locked nucleic acid antisense oligonucleotides (LNA) could be targeted, particularly, the 5′URT or sections of the Spike molecule, for both COVID-19 prevention and therapy [190–192].

Therefore, investigations on how to therapeutically prevent, attenuate, or reverse the epigenetic alterations, how to design specific pharmacological tools, and when/where to intervene by examining the epigenetic effects of metabolism on genes, pathways, and genomes should be done vigorously. Above all, the enzymes in charge of the epigenetic changes constitute a fascinating area of research for new therapeutic targets to treat COVID-19.

13. Conclusion

COVID-19 is a viral peril to humankind and also a leading cause of morbidity and death, which has become a pandemic as it infected almost every other person globally. Significant research implies that the aberrant immune reaction is driven by an evolutionary arms race and molecular interactions between the virus and the host's epigenetic environment. A further concern is whether SARS-CoV-2 has evolved to evade host immune reactions by altering the epigenetic machinery and subverting the host's replication, transcription, and proteomics programmes. The information compiled and reviewed here amply illustrates that RNA viruses like SARS-CoV-2 possess a molecular entity that allows them to sabotage the epigenetic architecture of their hosts in an attempt to dodge innate immunity. Therefore, future research on the reversible nature of epigenetic alterations holds the potential to prevent the virus from being able to infect host cells. It will be possible to forecast a pharmaceutical target for treatment efficacy and understand the epigenetic landscape of the immune response induced by SARS-CoV-2 with the integration of the epigenetically technological method.

Abbreviations

COVID-19	Coronavirus disease 19
SARS-CoV-2	Respiratory Syndrome coronavirus-2
HDACs	histone deacetylases
CoVs	corona viruses
(MERS)-CoV	Middle Eastern respiratory syndrome
Nsp	non-structural proteins

ACE2	angiotensin-converting enzyme 2
RBD	receptor-binding domain
TMPRSS2	transmembrane serine protease 2
CpG	5′-C-phosphate-G-3′
DNMTs	DNA methyltransferases
lncRNAs	long non-coding RNAs
ISGs	interferon secreting genes
HAT1	histone acetyltransferase1
KDM5B	lysine demethylase 5B
H3K4me	histone methylation
H3K27ac	histone acetylation
H3K4	H3's lysine 4
SIRT1	Sirtuin 1
XCI	X chromosome inactivation
Xic	X-inactivation centre
PADs	peptidyl arginine deiminases
NETs	neutrophil extracellular traps
PD1	programmed cell death protein-1
TIM3	T cell immunoglobulin domain and mucin domain-3
NKG2A	killer cell lectin-like receptor subfamily C member 1
STAT	signal transducer and activator of transcription
TRMT1	tRNA methyltransferase 1
NLRP3	NLR family pyrin domain containing 3
USP13	ubiquitin-specific peptidase 13
MCP1	monocyte chemoattractant protein
MIP1A	macrophage inflammatory protein 1-α
G-CSF	granulocyte-colony stimulating factor
ARDS	acute respiratory distress syndrome

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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References

[1] S.-u.-S. Mattoo, et al., Escape and over-activation of innate immune responses by SARS-CoV-2: two faces of a coin, Viruses 14 (3) (2022) 530.
[2] D. Jiménez, M. Torres Arias, Immunouniverse of SARS-CoV-2, Immunol. Med. (2022) 1–39.
[3] . D. Koiri et al, Phytochemicals as therapeutics against COVID-19: An in-silico study.
[4] M. Salgado-Albarrán, et al., Comparative transcriptome analysis reveals key epigenetic targets in SARS-CoV-2 infection, npj Syst. Biol. Applic. 7 (1) (2021) 1–14.
[5] N. Saksena, S.R. Bonam, M. Miranda-Saksena, Epigenetic lens to visualize the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in COVID-19 pandemic, Front. Genet. 12 (2021), 581726.
[6] Y. Huang, et al., Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19, Acta Pharmacol. Sin. 41 (9) (2020) 1141–1149.
[7] M.-Y. Wang, et al., SARS-CoV-2: structure, biology, and structure-based therapeutics development, Front. Cell. Infect. Microbiol. (2020) 724.
[8] X. Xia, Domains and functions of spike protein in Sars-Cov-2 in the context of vaccine design, Viruses 13 (1) (2021) 109.
[9] L. Du, et al., The spike protein of SARS-CoV—a target for vaccine and therapeutic development, Nat. Rev. Microbiol. 7 (3) (2009) 226–236.
[10] A.A.T. Naqvi, et al., Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: structural genomics approach, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1866 (10) (2020), 165878.
[11] D. Schoeman, B.C. Fielding, Coronavirus envelope protein: current knowledge, Virol. J. 16 (1) (2019) 1–22.
[12] L. Kuo, K.R. Hurst, P.S. Masters, Exceptional flexibility in the sequence requirements for coronavirus small envelope protein function, J. Virol. 81 (5) (2007) 2249–2262.
[13] V.S. Mandala, et al., Structure and drug binding of the SARS-CoV-2 envelope protein transmembrane domain in lipid bilayers, Nat. Struct. Mol. Biol. 27 (12) (2020) 1202–1208.
[14] E. Alsaadi, I. Jones, Membrane binding proteins of coronaviruses [Internet], Future Med. 14 (4) (2019 Apr 1) 275–286 [cited 2020 Jun 10].
[15] S. Thomas, The structure of the membrane protein of SARS-CoV-2 resembles the sugar transporter SemiSWEET, Pathog. Immun. 5 (1) (2020) 342.
[16] T. Tang, et al., Coronavirus membrane fusion mechanism offers a potential target for antiviral development, Antivir. Res. 178 (2020), 104792.
[17] J. Liu, et al., The membrane protein of severe acute respiratory syndrome coronavirus acts as a dominant immunogen revealed by a clustering region of novel functionally and structurally defined cytotoxic T-lymphocyte epitopes, J. Infect. Dis. 202 (8) (2010) 1171–1180.
[18] B.W. Neuman, M.J. Buchmeier, Supramolecular architecture of the coronavirus particle, Adv. Virus Res. 96 (2016) 1–27.
[19] Y.-Q. Min, et al., SARS-CoV-2 nsp1: bioinformatics, potential structural and functional features, and implications for drug/vaccine designs, Front. Microbiol. (2020) 2393.
[20] F.K. Yoshimoto, The proteins of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2 or n-COV19), the cause of COVID-19, Protein J. 39 (3) (2020) 198–216.
[21] J. Lei, Y. Kusov, R. Hilgenfeld, Nsp3 of coronaviruses: structures and functions of a large multi-domain protein, Antivir. Res. 149 (2018) 58–74.
[22] L.A. Armstrong, et al., Biochemical characterization of protease activity of Nsp3 from SARS-CoV-2 and its inhibition by nanobodies, PloS one 16 (7) (2021), e0253364.
[23] K. Anand, et al., Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra α-helical domain, EMBO J. 21 (13) (2002) 3213–3224.
[24] A. Kumar, et al., Investigating the conformational dynamics of SARS-CoV-2 NSP6 protein with emphasis on non-transmembrane 91–112 & 231–290 regions, Microb. Pathog. 161 (2021), 105236.
[25] A.J. Te Velthuis, S.H. Van Den Worm, E.J. Snijder, The SARS-coronavirus nsp7+nsp8 complex is a unique multimeric RNA polymerase capable of both de novo initiation and primer extension, Nucleic Acids Res. 40 (4) (2012) 1737–1747.
[26] P. Kumar, et al., The nonstructural protein 8 (nsp8) of the SARS coronavirus interacts with its ORF6 accessory protein, Virology 366 (2) (2007) 293–303.
[27] G. Sutton, et al., The nsp9 replicase protein of SARS-coronavirus, structure and functional insights, Structure 12 (2) (2004) 341–353.
[28] M.-P. Egloff, et al., The severe acute respiratory syndrome-coronavirus replicative protein nsp9 is a single-stranded RNA-binding subunit unique in the RNA virus world, Proc. Natl. Acad. Sci. 101 (11) (2004) 3792–3796.
[29] M. Bouvet, et al., Coronavirus Nsp10, a critical co-factor for activation of multiple replicative enzymes, J. Biol. Chem. 289 (37) (2014) 25783–25796.
[30] J.S. Joseph, et al., Crystal structure of nonstructural protein 10 from the severe acute respiratory syndrome coronavirus reveals a novel fold with two zinc-binding motifs, J. Virol. 80 (16) (2006) 7894–7901.
[31] K. Gadhave, et al., in: NSP 11 of SARS-CoV-2 is an intrinsically disordered protein. bioRxiv 10(2020.10), 2020, p. 07.330068.
[32] Q. Peng, et al., Structural and biochemical characterization of the nsp12-nsp7-nsp8 core polymerase complex from SARS-CoV-2, Cell Rep. 31 (11) (2020), 107774.
[33] A.J. Te Velthuis, et al., The RNA polymerase activity of SARS-coronavirus nsp12 is primer dependent, Nucleic Acids Res. 38 (1) (2010) 203–214.
[34] T. Shu, et al., SARS-coronavirus-2 Nsp13 possesses NTPase and RNA helicase activities that can be inhibited by bismuth salts, Virol. Sin. 35 (3) (2020) 321–329.
[35] M. Tahir, Coronavirus genomic nsp14-ExoN, structure, role, mechanism, and potential application as a drug target, J. Med. Virol. 93 (7) (2021) 4258–4264.
[36] M.N. Frazier, et al., Characterization of SARS2 Nsp15 nuclease activity reveals it's mad about U, Nucleic Acids Res. 49 (17) (2021) 10136–10149.
[37] N. Vithani, et al., SARS-CoV-2 Nsp16 activation mechanism and a cryptic pocket with pan-coronavirus antiviral potential, Biophys. J. 120 (14) (2021) 2880–2889.
[38] Y. Wan, et al., Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus, J. Virol. 94 (7) (2020), e00127-20.
[39] P. V'kovski, et al., Coronavirus biology and replication: implications for SARS-CoV-2, Nat. Rev. Microbiol. 19 (3) (2021) 155–170.

[40] M.A. Tortorici, D. Veesler, Structural insights into coronavirus entry, Adv. Virus Res. 105 (2019) 93–116.
[41] F. Li, Structure, function, and evolution of coronavirus spike proteins, Annu. Rev. Virol. 3 (2016) 237–261.
[42] M. Letko, A. Marzi, V. Munster, Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses, Nat. Microbiol. 5 (4) (2020) 562–569.
[43] M. Hoffmann, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280. e8.
[44] R. Sen, et al., Epigenetic mechanisms influencing COVID-19, Genome 64 (4) (2021) 372–385.
[45] I. Astuti, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response, Diabetes Metab. Syndr. Clin. Res. Rev. 14 (4) (2020) 407–412.
[46] J. Ziebuhr, Molecular biology of severe acute respiratory syndrome coronavirus, Curr. Opin. Microbiol. 7 (4) (2004) 412–419.
[47] D. Yang, J.L. Leibowitz, The structure and functions of coronavirus genomic 3′ and 5′ ends, Virus Res. 206 (2015) 120–133.
[48] B. Malone, et al., Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design, Nat. Rev. Mol. Cell Biol. 23 (1) (2022) 21–39.
[49] D. Brian, R. Baric, Coronavirus genome structure and replication, in: Coronavirus Replication And Reverse Genetics, 2005, pp. 1–30.
[50] M.A. Shereen, et al., COVID-19 infection: origin, transmission, and characteristics of human coronaviruses, J. Adv. Res. 24 (2020) 91.
[51] H. Iqbal, et al., The emergence of novel-coronavirus and its replication cycle-an overview, J. Pure Appl. Microbiol. 14 (1) (2020) 13–16.
[52] D.E. Handy, R. Castro, J. Loscalzo, Epigenetic modifications: basic mechanisms and role in cardiovascular disease, Circulation 123 (19) (2011) 2145–2156.
[53] A.P. Bird, CpG-rich islands and the function of DNA methylation, Nature 321 (6067) (1986) 209–213.
[54] W. Reik, Stability and flexibility of epigenetic gene regulation in mammalian development, Nature 447 (7143) (2007) 425–432.
[55] R.S. Illingworth, A.P. Bird, CpG islands–'a rough guide', FEBS Lett. 583 (11) (2009) 1713–1720.
[56] L. Shen, et al., Genome-wide profiling of DNA methylation reveals a class of normally methylated CpG island promoters, PLoS Genet. 3 (10) (2007), e181.
[57] R. Lister, et al., Human DNA methylomes at base resolution show widespread epigenomic differences, Nature 462 (7271) (2009) 315–322.
[58] H. Leonhardt, et al., A targeting sequence directs DNA methyltransferase to sites of DNA replication in mammalian nuclei, Cell 71 (5) (1992) 865–873.
[59] J. Loscalzo, D.E. Handy, Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series), Pulm. Circ. 4 (2) (2014) 169–174.
[60] S.K. Patra, Ras regulation of DNA-methylation and cancer, Exp. Cell Res. 314 (6) (2008) 1193–1201.
[61] S.K. Patra, M. Szyf, DNA methylation-mediated nucleosome dynamics and oncogenic Ras signaling: Insights from FAS, FAS ligand and RASSF1A, FEBS J. 275 (21) (2008) 5217–5235.
[62] S.K. Patra, et al., Demethylation of (Cytosine-5-C-methyl) DNA and regulation of transcription in the epigenetic pathways of cancer development, Cancer Metastasis Rev. 27 (2) (2008) 315–334.
[63] T. Kouzarides, Chromatin modifications and their function, Cell 128 (4) (2007) 693–705.
[64] C. Martin, Y. Zhang, The diverse functions of histone lysine methylation, Nat. Rev. Mol. Cell Biol. 6 (11) (2005) 838–849.
[65] T. Jenuwein, C.D. Allis, Translating the histone code, Science 293 (5532) (2001) 1074–1080.
[66] C.E. Berndsen, J.M. Denu, Catalysis and substrate selection by histone/protein lysine acetyltransferases, Curr. Opin. Struct. Biol. 18 (6) (2008) 682–689.
[67] H.S. Mellert, S.B. McMahon, Biochemical pathways that regulate acetyltransferase and deacetylase activity in mammalian cells, Trends Biochem. Sci. 34 (11) (2009) 571–578.
[68] S. Michan, D. Sinclair, Sirtuins in mammals: insights into their biological function, Biochem. J. 404 (1) (2007) 1–13.
[69] E. Metzger, et al., LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription, Nature 437 (7057) (2005) 436–439.
[70] Y.-I. Tsukada, et al., Histone demethylation by a family of JmjC domain-containing proteins, Nature 439 (7078) (2006) 811–816.
[71] P. Völkel, P.-O. Angrand, The control of histone lysine methylation in epigenetic regulation, Biochimie 89 (1) (2007) 1–20.
[72] M. Deb, et al., Chromatin dynamics: H3K4 methylation and H3 variant replacement during development and in cancer, Cell. Mol. Life Sci. 71 (18) (2014) 3439–3463.
[73] A. Behura, et al., miRNAs and its regulatory role on autophagy in tumor microenvironment, in: Autophagy in Tumor And Tumor Microenvironment, Springer, 2020, pp. 77–101.
[74] T.R. Mercer, M.E. Dinger, J.S. Mattick, Long non-coding RNAs: insights into functions, Nat. Rev. Genet. 10 (3) (2009) 155–159.
[75] N. Schonrock, R.P. Harvey, J.S. Mattick, Long noncoding RNAs in cardiac development and pathophysiology, Circ. Res. 111 (10) (2012) 1349–1362.
[76] D.H. Kim, et al., MicroRNA-directed transcriptional gene silencing in mammalian cells, Proc. Natl. Acad. Sci. 105 (42) (2008) 16230–16235.
[77] D.H. Kim, et al., Argonaute-1 directs siRNA-mediated transcriptional gene silencing in human cells, Nat. Struct. Mol. Biol. 13 (9) (2006) 793–797.
[78] M.J. Luteijn, R.F. Ketting, PIWI-interacting RNAs: from generation to transgenerational epigenetics, Nat. Rev. Genet. 14 (8) (2013) 523–534.
[79] P. Mehta, et al., COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (10229) (2020) 1033–1034.
[80] G. Egger, et al., Epigenetics in human disease and prospects for epigenetic therapy, Nature 429 (6990) (2004) 457–463.
[81] A. Schäfer, R.S. Baric, Epigenetic landscape during coronavirus infection, Pathogens 6 (1) (2017) 8.
[82] R. Rathod, et al., Methylation of host genes associated with coronavirus infection from birth to 26 years, Genes 12 (8) (2021) 1198.
[83] N. Saksena, S.R. Bonam, M. Miranda-Saksena, Epigenetic lens to visualize the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in COVID-19 pandemic, Front. Genet. 12 (2021) 291.
[84] S. Chlamydas, A.G. Papavassiliou, C. Piperi, Epigenetic mechanisms regulating COVID-19 infection, Epigenetics 16 (3) (2021) 263–270.
[85] B.G. Pinto, et al., ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19, J. Infect. Dis. 222 (4) (2020) 556–563.
[86] J. Yang, et al., ACE2 correlated with immune infiltration serves as a prognostic biomarker in endometrial carcinoma and renal papillary cell carcinoma: implication for COVID-19, Aging (Albany NY) 12 (8) (2020) 6518.
[87] A.H. Sawalha, et al., Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients, Clin. Immunol. 215 (2020), 108410.
[88] L. Holmes Jr., et al., DNA methylation of candidate genes (ACE II, IFN-γ, AGTR 1, CKG, ADD1, SCNN1B and TLR2) in essential hypertension: a systematic review and quantitative evidence synthesis, Int. J. Environ. Res. Public Health 16 (23) (2019) 4829.
[89] C. Muus, et al., Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells, BioRxiv (2020).
[90] V.D. Menachery, et al., MERS-CoV and H5N1 influenza virus antagonize antigen presentation by altering the epigenetic landscape, Proc. Natl. Acad. Sci. 115 (5) (2018) E1012–E1021.
[91] M.J. Corley, L.C. Ndhlovu, 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, 2020.
[92] M. Beato, P. Sharma, Peptidyl arginine deiminase 2 (PADI2)-mediated arginine citrullination modulates transcription in cancer, Int. J. Mol. Sci. 21 (4) (2020) 1351.
[93] G. Rogers, D. Simmonds, Content of citrulline and other amino-acids in a protein of hair follicles, Nature 182 (4629) (1958) 186–187.
[94] F.G. Mastronardi, et al., Increased citrullination of histone H3 in multiple sclerosis brain and animal models of demyelination: a role for tumor necrosis factor-induced peptidylarginine deiminase 4 translocation, J. Neurosci. 26 (44) (2006) 11387–11396.
[95] M. Leshner, et al., PAD4 mediated histone hypercitrullination induces heterochromatin decondensation and chromatin unfolding to form neutrophil extracellular trap-like structures, Front. Immunol. 3 (2012) 307.
[96] E.R. Vossenaar, et al., Expression and activity of citrullinating peptidylarginine deiminase enzymes in monocytes and macrophages, Ann. Rheum. Dis. 63 (4) (2004) 373–381.
[97] R. Khandpur, et al., NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis, Sci. Transl. Med. 5 (178) (2013), p. 178ra40-178ra40.
[98] M. Szturmowicz, U. Demkow, Neutrophil extracellular traps (NETs) in severe SARS-CoV-2 lung disease, Int. J. Mol. Sci. 22 (16) (2021) 8854.
[99] J. Huckriede, et al., Histone H3 cleavage in severe COVID-19 ICU patients, Front. Cell. Infect. Microbiol. 11 (2021), 694186.
[100] Y. Yokoyama, et al., Circulating histone H3 levels in septic patients are associated with coagulopathy, multiple organ failure, and death: a single-center observational study, Thromb. J. 17 (1) (2019) 1–7.
[101] T.A. Fuchs, A.A. Bhandari, D.D. Wagner, Histones induce rapid and profound thrombocytopenia in mice, Blood 118 (13) (2011) 3708–3714.
[102] M. Nakahara, et al., Recombinant thrombomodulin protects mice against histone-induced lethal thromboembolism, PloS one 8 (9) (2013), e75961.
[103] L. Yang, et al., COVID-19: immunopathogenesis and immunotherapeutics, Signal Transduct. Target. Ther. 5 (1) (2020) 1–8.
[104] N. Fathi, N. Rezaei, Lymphopenia in COVID-19: therapeutic opportunities, Cell Biol. Int. 44 (9) (2020) 1792–1797.
[105] Y. Liu, et al., Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019, MedRxiv (2020).
[106] G. Lippi, M. Plebani, Laboratory abnormalities in patients with COVID-2019 infection, Clin. Chem. Lab. Med. 58 (7) (2020) 1131–1134.
[107] M. Croft, et al., The significance of OX40 and OX40L to T-cell biology and immune disease, Immunol. Rev. 229 (1) (2009) 173–191.
[108] D. Laderach, et al., 4–1BB co-stimulation enhances human CD8+ T cell priming by augmenting the proliferation and survival of effector CD8+ T cells, Int. Immunol. 14 (10) (2002) 1155–1167.
[109] I. Thevarajan, et al., Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19, Nat. Med. 26 (4) (2020) 453–455.
[110] N. Chen, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.

[111] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China, Lancet 395 (10223) (2020) 497–506.
[112] A. Behura, et al., ESAT-6 modulates calcimycin-induced autophagy through microRNA-30a in mycobacteria infected macrophages, J. Infect. 79 (2) (2019) 139–152.
[113] D.W. Trobaugh, W.B. Klimstra, MicroRNA regulation of RNA virus replication and pathogenesis, Trends Mol. Med. 23 (1) (2017) 80–93.
[114] A. Głobińska, M. Pawełczyk, M.L. Kowalski, MicroRNAs and the immune response to respiratory virus infections, Expert. Rev. Clin. Immunol. 10 (7) (2014) 963–971.
[115] B.B. Süt, Epigenetic regulation mechanisms in viral infections: a special focus on COVID-19, in: Biotechnology to Combat COVID-19, IntechOpen, 2021.
[116] D. Fruci, R. Rota, A. Gallo, The role of HCMV and HIV-1 microRNAs: processing, and mechanisms of action during viral infection, Front. Microbiol. 8 (2017) 689.
[117] Y. Zhuo, et al., miRNAs: biogenesis, origin and evolution, functions on virus-host interaction, Cell. Physiol. Biochem. 32 (3) (2013) 499–510.
[118] F.W. Lai, et al., Human coronavirus OC43 nucleocapsid protein binds microRNA 9 and potentiates NF-κB activation, J. Virol. 88 (1) (2014) 54–65.
[119] M.A.-A.-K. Khan, et al., Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19, Front. Genet. 11 (2020) 765.
[120] J.B. De Sanctis, et al., Importance of miRNA in SARS-CoV2 infection, Gac. Med. Caracas 128 (1S) (2020) S17–S22.
[121] E. Crimi, et al., Epigenetic susceptibility to severe respiratory viral infections and its therapeutic implications: a narrative review, Br. J. Anaesth. 125 (6) (2020) 1002–1017.
[122] E.D. Arisan, et al., The prediction of miRNAs in SARS-CoV-2 genomes: hsa-miR databases identify 7 key miRs linked to host responses and virus pathogenicity-related KEGG pathways significant for comorbidities, Viruses 12 (6) (2020) 614.
[123] F. Abedi, et al., MicroRNAs and SARS-CoV-2 life cycle, pathogenesis, and mutations: biomarkers or therapeutic agents? Cell Cycle 20 (2) (2021) 143–153.
[124] G. Pontecorvi, et al., microRNAs as new possible actors in gender disparities of COVID-19 pandemic, Acta Physiol. 230 (1) (2020), e13538.
[125] G. Ragia, V.G. Manolopoulos, Assessing COVID-19 susceptibility through analysis of the genetic and epigenetic diversity of ACE2-mediated SARS-CoV-2 entry, Pharmacogenomics 21 (18) (2020) 1311–1329.
[126] M.A.-A.-K. Khan, A.B.M.M.K. Islam, SARS-CoV-2 proteins exploit host's genetic and epigenetic mediators for the annexation of key host signaling pathways, Front. Mol. Biosci. 7 (2021), 598583.
[127] A. Zarubin, et al., Structural variability, expression profile, and pharmacogenetic properties of TMPRSS2 gene as a potential target for COVID-19 therapy, Genes 12 (1) (2020) 19.
[128] S.G. AbdelHamid, et al., Deciphering epigenetic (s) role in modulating susceptibility to and severity of COVID-19 infection and/or outcome: a systematic rapid review, Environ. Sci. Pollut. Res. 28 (39) (2021) 54209–54221.
[129] R. Srivastava, et al., Role of SARS-CoV-2 in altering the RNA-binding protein and miRNA-directed post-transcriptional regulatory networks in humans, Int. J. Mol. Sci. 21 (19) (2020) 7090.
[130] M. Beidas, W. Chehadeh, Effect of human coronavirus OC43 structural and accessory proteins on the transcriptional activation of antiviral response elements, Intervirology 61 (1) (2018) 30–35.
[131] H. Henzinger, et al., Non-coding RNAs and SARS-related coronaviruses, Viruses 12 (12) (2020) 1374.
[132] R. Vishnubalaji, H. Shaath, N.M. Alajez, Protein coding and long noncoding RNA (lncRNA) transcriptional landscape in SARS-CoV-2 infected bronchial epithelial cells highlight a role for interferon and inflammatory response, Genes 11 (7) (2020) 760.
[133] D. Qu, et al., Long noncoding RNA MALAT1 releases epigenetic silencing of HIV-1 replication by displacing the polycomb repressive complex 2 from binding to the LTR promoter, Nucleic Acids Res. 47 (6) (2019) 3013–3027.
[134] F. McCluggage, A.H. Fox, Paraspeckle nuclear condensates: global sensors of cell stress? Bioessays 43 (5) (2021), 2000245.
[135] D.E. Gordon, et al., A SARS-CoV-2 protein interaction map reveals targets for drug repurposing, Nature 583 (7816) (2020) 459–468.
[136] P. Xu, et al., NOS1 inhibits the interferon response of cancer cells by S-nitrosylation of HDAC2, J. Exp. Clin. Cancer Res. 38 (1) (2019) 1–16.
[137] I.J. Marié, H.-M. Chang, D.E. Levy, HDAC stimulates gene expression through BRD4 availability in response to IFN and in interferonopathies, J. Exp. Med. 215 (12) (2018) 3194–3212.
[138] G.A. Josling, et al., The role of bromodomain proteins in regulating gene expression, Genes 3 (2) (2012) 320–343.
[139] Y. Konno, et al., SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant, Cell Rep. 32 (12) (2020), 108185.
[140] M. Fakhrolmobasheri, A. Shiravi, M. Zeinalian, SARS-CoV-2 interaction with human DNA methyl transferase 1: a potential risk for increasing the incidence of later chronic diseases in the survived patients, Int. J. Prev. Med. (2022) 13.
[141] M. Bouhaddou, et al., The global phosphorylation landscape of SARS-CoV-2 infection, Cell 182 (3) (2020) 685–712.e19.
[142] A. Behura, et al., ESAT-6 impedes IL-18 mediated phagosome lysosome fusion via microRNA-30a upon Calcimycin treatment in mycobacteria infected macrophages, Int. Immunopharmacol. 101 (2021), 108319.
[143] C. Qin, et al., Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan,China, Clin. Infect. Dis. 71 (15) (2020) 762–768.
[144] A. Fara, et al., Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines, Open Biol. 10 (9) (2020), 200160.
[145] A. Muhammad, et al., Epigenetic modifications associated with genes implicated in cytokine storm: the potential biotherapeutic effects of vitamins and minerals in COVID-19, J. Food Biochem. 46 (5) (2022), e14079.
[146] H. Shakoor, et al., Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas 143 (2021) 1–9.
[147] J. Liu, et al., Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients, EBioMedicine 55 (2020), 102763.
[148] R. El Baba, G. Herbein, Management of epigenomic networks entailed in coronavirus infections and COVID-19, Clin. Epigenetics 12 (1) (2020) 1–12.
[149] S. Atlante, et al., The epigenetic implication in coronavirus infection and therapy, Clin. Epigenetics 12 (1) (2020) 1–12.
[150] C.-C. Lai, et al., Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths, J. Microbiol. Immunol. Infect. 53 (3) (2020) 404–412.
[151] M. Poppe, et al., The NF-κB-dependent and-independent transcriptome and chromatin landscapes of human coronavirus 229E-infected cells, PLoS Pathog. 13 (3) (2017), e1006286.
[152] G. Abdolmaleki, et al., A comparison between SARS-CoV-1 and SARS-CoV2: an update on current COVID-19 vaccines, DARU J. Pharm. Sci. (2022) 1–28.
[153] H.K. Siddiqi, M.R. Mehra, COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal, J. Heart Lung Transplant. 39 (5) (2020) 405–407.
[154] I. Fricke-Galindo, R. Falfán-Valencia, Genetics insight for COVID-19 susceptibility and severity: a review, Front. Immunol. 12 (2021), 622176.
[155] A. Nguyen, et al., Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2, J. Virol. 94 (13) (2020) e00510–e00520.
[156] M.M. Idris, et al., Down regulation of defensin genes during SARS-CoV-2 infection, Acta Virol. 66 (3) (2022) 249–253.
[157] B.P. Jit, et al., An immune epigenetic insight to COVID-19 infection, Epigenomics 13 (06) (2021) 465–480.
[158] S.K. Patra, M. Szyf, Epigenetic perspectives of COVID-19: virus infection to disease progression and therapeutic control, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1868 (12) (2022), 166527.
[159] R. Zang, et al., TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes, Sci. Immunol. 5 (47) (2020) eabc3582.
[160] I.G. Ovsyannikova, et al., The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity, Immunol. Rev. 296 (1) (2020) 205–219.
[161] S. Ghafouri-Fard, et al., Effects of host genetic variations on response to, susceptibility and severity of respiratory infections, Biomed. Pharmacother. 128 (2020), 110296.
[162] . D. Corley Methylation Analysis of the COVID-19 Host Cell Receptor. Angiotensin I Converting Enzyme. 2: p. 2020030295.
[163] Y. Zhao, et al., Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2, Am. J. Respir. Crit. Care Med. 202 (5) (2020) 756–759.
[164] A.J. Eastman, et al., Epigenetic stabilization of DC and DC precursor classical activation by TNFα contributes to protective T cell polarization, Sci. Adv. 5 (12) (2019) eaaw9051.
[165] U. Weiss, et al., Inhibition of HDAC enzymes contributes to differential expression of pro-inflammatory proteins in the TLR-4 signaling cascade, Int. J. Mol. Sci. 21 (23) (2020) 8943.
[166] V. Singh, Can vitamins, as epigenetic modifiers, enhance immunity in COVID-19 patients with non-communicable disease? Curr. Nutr. Rep. 9 (3) (2020) 202–209.
[167] N. Vyas, et al., Vitamin D in prevention and treatment of COVID-19: current perspective and future prospects, J. Am. Coll. Nutr. 40 (7) (2021) 632–645.
[168] M. Ducasse, M.A. Brown, Epigenetic aberrations and cancer, Mol. Cancer 5 (1) (2006) 1–10.
[169] L. Zhu, et al., Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression, Am. J. Transplant. 20 (7) (2020) 1859–1863.
[170] L. Pruimboom, Methylation pathways and SARS-CoV-2 lung infiltration and cell membrane-virus fusion are both subject to epigenetics, Front. Cell. Infect. Microbiol. 10 (290) (2020) 2020.
[171] J. Rhodes, et al., Perspective: vitamin D deficiency and COVID-19 severity–plausibly linked by latitude, ethnicity, impacts on cytokines. ACE2, and thrombosis (R1), J. Intern. Med. 289 (1) (2021) 97–115.
[172] M. Cutolo, S. Paolino, V. Smith, Evidences for a protective role of vitamin D in COVID-19, BMJ Spec. J. 6 (3) (2020), e001454.
[173] J.P. Bilezikian, et al., Mechanisms in endocrinology: vitamin D and COVID-19, Eur. J. Endocrinol. 183 (5) (2020) R133–R147.
[174] A.C.R. Souza, et al., Zinc, vitamin D and vitamin C: perspectives for COVID-19 with a focus on physical tissue barrier integrity, Front. Nutr. (2020) 295.
[175] A. Daneshkhah, et al., Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients, Aging Clin. Exp. Res. 32 (10) (2020) 2141–2158.
[176] J.F.-W. Chan, et al., Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan, Emerg. Microbes Infect. 9 (1) (2020) 221–236.
[177] N. Zhang, et al., Recent advances in the detection of respiratory virus infection in humans, J. Med. Virol. 92 (4) (2020) 408–417.

[178] E.-W. Son, et al., Vitamin C blocks TNF-α-induced NF-kB activation and ICAM-1 expression in human neuroblastoma cells, Arch. Pharm. Res. 27 (10) (2004) 1073–1079.
[179] A. Pal, et al., Zinc and COVID-19: basis of current clinical trials, Biol. Trace Elem. Res. 199 (8) (2021) 2882–2892.
[180] E.R. Sang, et al., Epigenetic evolution of ACE2 and IL-6 genes: non-canonical interferon-stimulated genes correlate to COVID-19 susceptibility in vertebrates, Genes 12 (2) (2021) 154.
[181] M.T. Beigmohammadi, et al., The association between serum levels of micronutrients and the severity of disease in patients with COVID-19, Nutrition 91 (2021), 111400.
[182] G. Schett, Physiological effects of modulating the interleukin-6 axis, Rheumatology 57 (suppl_2) (2018) ii43–ii50.
[183] D.L. McCartney, et al., Epigenetic signatures of starting and stopping smoking, EBioMedicine 37 (2018) 214–220.
[184] N. Curtin, et al., Repositioning PARP inhibitors for SARS-CoV-2 infection (COVID-19); a new multi-pronged therapy for acute respiratory distress syndrome? Br. J. Pharmacol. 177 (16) (2020) 3635–3645.
[185] P.A. Van Dam, et al., SARS-CoV-2 and cancer: are they really partners in crime? Cancer Treat. Rev. 89 (2020), 102068.
[186] S. Ayaz, F. Crea, Targeting SARS-CoV-2 using polycomb inhibitors as antiviral agents, Future Med. (2020) 811–812.
[187] Y. Fang, et al., Natural products as LSD1 inhibitors for cancer therapy, Acta Pharm. Sin. B 11 (3) (2021) 621–631.
[188] C.-J. Wu, Y.-L. Chan, Antiviral applications of RNAi for coronavirus, Expert Opin. Investig. Drugs 15 (2) (2006) 89–97.
[189] A. Levanova, M.M. Poranen, RNA interference as a prospective tool for the control of human viral infections, Front. Microbiol. (2018) 2151.
[190] A. Baldassarre, et al., Potential use of noncoding RNAs and innovative therapeutic strategies to target the 5'UTR of SARS-CoV-2, Epigenomics 12 (15) (2020) 1349–1361.
[191] Y. Zhang, et al., Silencing SARS-CoV spike protein expression in cultured cells by RNA interference, FEBS Lett. 560 (1–3) (2004) 141–146.
[192] B.-J. Zheng, et al., Prophylactic and therapeutic effects of small interfering RNA targeting SARS-coronavirus, Antivir. Ther. 9 (3) (2004) 365–374.