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Epigenetic perspectives of COVID-19: Virus infection to disease progression and therapeutic control

Samir Kumar Patra [a,*], Moshe Szyf [b]

[a] Epigenetics and Cancer Research Laboratory, Biochemistry and Molecular Biology Group, Department of Life Science, National Institute of Technology, Rourkela 769008, Odisha, India
[b] Department of Pharmacology & Therapeutics, McIntyre Medical Sciences Building, McGill University, Montreal, QC H3G 1Y6, Canada

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ABSTRACT

COVID-19 has caused numerous deaths as well as imposed social isolation and upheaval world-wide. Although, the genome and the composition of the virus, the entry process and replication mechanisms are well investigated from by several laboratories across the world, there are many unknown remaining questions. For example, what are the functions of membrane lipids during entry, packaging and exit of virus particles? Also, the metabolic aspects of the infected tissue cells are poorly understood. In the course of virus replication and formation of virus particles within the host cell, the enhanced metabolic activities of the host is directly proportional to viral loads. The epigenetic landscape of the host cells is also altered, particularly the expression/repression of genes associated with cellular metabolism as well as cellular processes that are antagonistic to the virus. Metabolic pathways are enzyme driven processes and the expression profile and mechanism of regulations of the respective genes encoding those enzymes during the course of pathogen invasion might be highly informative on the course of the disease. Recently, the metabolic profile of the patients' sera have been analysed from few patients. In view of this, and to gain further insights into the roles that epigenetic mechanisms might play in this scenario in regulation of metabolic pathways during the progression of COVID-19 are discussed and summarised in this contribution for ensuring best therapy.

1. Introduction

Sudden outbreak of severe acute respiratory syndrome corona virus clade-2 (SARS-CoV-2) has affected all aspects of global human society, including medical, societal, economy & business, research & education, games & sports, transport and others as well. The virus, SARS-CoV-2 belongs to the subgenus Sarbecovirus of the genus Betacoronavirus similar to SARS-CoV. However, they are genetically distinct from each other with similar receptor-binding domain structure with key amino acid variation of several residues [1,2]. The genome is single-stranded positive-sense RNA (ss(+)RNA) of ~30kb size with 5′-cap structure and 3′-poly-A tail [3] and it has no less than 10 open reading frames (ORFs). It directly translates polyproteins 1a/1ab (pp1a/pp1ab), which are cleaved subsequently to several (~16) non-structural proteins (nsps). Subgenomic RNAs encode structural proteins; envelope, membrane, spike, nucleocapsid and other accessory proteins [2,3].

2. The replication cycle of SARS-CoV-2

SARS-CoV-2 is a ss(+)RNA virus, and as of yet there is no evidence that it integrates in the host genome during its life cycle (see Fig. 1). The classical epigenetic mechanisms; chromatin folding, unfolding and refolding by DNA methylations and a diversity of histone modifications of histones, as well as chromatin remodeling mechanisms [11,12] are not expected to be involved in corona virus growth and replication. However, there is evidence for direct epigenetic intervention in the viral genome through N6-methyladenosine modification of the viral genome [13] and human microRNAs (miRNA) targeting COVID-19 viral mRNA were postulated [14]. Cellular epigenetic processes indirectly regulate the severity of COVID-19 disease by regulating the immune response to COVID-19, epigenetic pathways of the host cell machineries that support the virus life cycle as well as the inflammatory responses that trigger damage to lung and other tissues at the severe phase of the disease. These mechanisms will be discussed in the subsequent sections.

* Corresponding author.
E-mail address: samirp@nitrkl.ac.in (S.K. Patra).

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2.1. The SARS-CoV-2 genome

In SARS-CoV-2 first two-third of the RNA encodes the mRNA that contains two open reading frames ORF1a/b that are directly translated to polyproteins. These polyproteins are processed by proteases to produce ~16 non-structural proteins (nsps). For the precise functions of each of the nsps along with the descriptions of structural proteins, the readers are directed into the link; https://swissmodel.expasy.org/repository/species/2697049 [15]. Auto-catalytically produced nsp5, from pp1a, functions as the main protease (MPro). MPro, then successively catalyses the production of other nsps from the PPab; among those, nsp12 is the core RNA dependent RNA polymerase (RDRP), which is assisted by nsp7 and nsp8 [16–18].

Although, several human miRNAs have putative targets in COVID-19 genome [13] and at least 10 ORFs operate [3] during replication of SARS-CoV-2; there is no experimental data that a miRNA does inhibit the translation of any of those ORF or remain silent forming a processing body (PB) or stress granule (SG) as of yet (for PB/SG; see [19,20]). There is no experimental report regarding PB/SG formation and silencing of host/virus mRNA by miRNA post-infection. RNA methylation at the exocyclic N-6 (NH2) adenine (N-6 mA) is a nuclear phenomenon, which is involved in splicing, mRNA export and rate of translation [21–25]. There is emerging evidence for an important role for N-6 mA in clinical manifestation of COVID-19 [26,27].

2.2. Host cell function during production of new virion particles following successful infection

There are many changes in the metabolic and nuclear activities of virus infected cell (Fig. 1). Approximate calculation implicates that, production of virion particles per infected cell (viral burst size is not applicable because virion come out by budding from the host cells) is about 104 to 105 [28,29]. Synthesis of this huge amount of virion particles exploits the cellular metabolic pathways [30,31], including glycolysis, amino acids and nucleotides biosynthesis. The genes of these metabolic enzymes are regulated by epigenetic mechanisms; either by both DNA methylation and histone modifications or by only histone modifications (see Fig. 1) or chromatin remodeling.

The high throughput synthesis of viral proteins, including nsps and structural proteins exert extreme demands on the capacity of the cells to enhance production of ribosomes biogenesis in the nucleolus [32], which in turn depends on increasing synthesis and supply of ribosomal proteins, which is contingent on increasing (i) the synthesis mRNA of the respective ribosomal proteins, (ii) splicing and nuclear export of mRNA to the cytosol, (iii) translation of the mRNA to proteins, (iv) transport of the proteins to the nucleus, specifically to the nucleolus, (v) simultaneous transcription of rDNA by RNAPolI and processing of pre-rRNA to rRNA in the nuclear-speckle and finally, assembly of ribosomes [33–39]. In view of this, the metabolic status of normal lung cells and tissues [40], expression profile of lung tissue markers [39], the metabolomic status of the system of COVID-19 victims from blood sera [41] and that of other cell/tissue types could play an important role in the patient response to COVID-19 infection [42].

Viral infection involves virion landing on the host cell surface creating a complex of it's envelop/spike proteins with membrane receptor(s) and subsequent penetration through the cell membrane and entry into the cytoplasm by endocytosis. Endocytosis requires overcoming a physical barrier, the actin meshwork, which is of considerable challenge for the virus [36] and it therefore involves the induction of actin cytoskeleton remodeling upon supplying nutrients and taking back

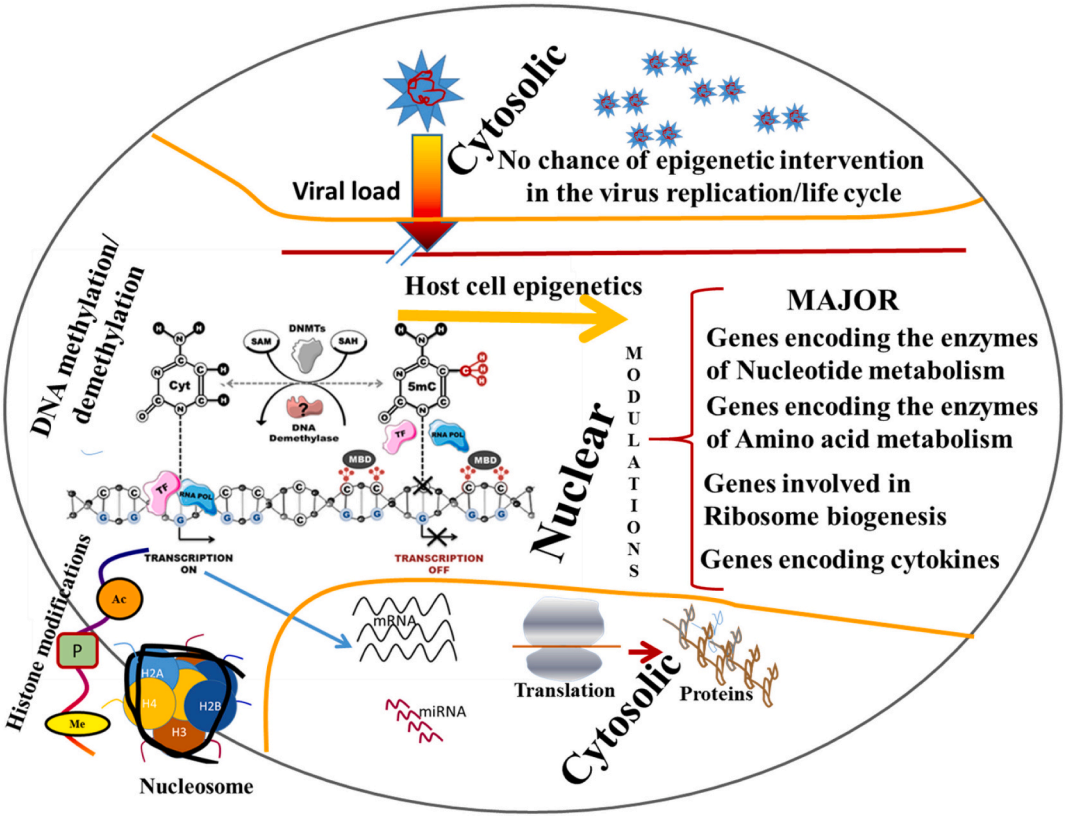

Fig. 1. Overall impression of the chromatin modifications mediated cellular epigenetics of the host cell under rapid replication and virion production. SARS-CoV-2 replication and assembly occur in the cytosol. There is huge requirement of nucleotides, amino acids, and cofactors and overall metabolic profile of the cell is tremendously affected by immunomodulation and altered signals imposed by the remodelled cellular environment imposed by the virus entry and replication cascades.

the waste materials for throwing out from the system through liver, kidney and faecal excretion. In case of COVID-19, the primary target of the virus is human lung cell [37–39]. In case of SARS-CoV and SARS-CoV-2 entry is driven by complex formation of viral Spike protein and host cell surface protein angiotensin-converting enzyme II (ACE2) and the processing of receptor binding domain (RBD) of ACE2 then catalysed by proteases TMPRSS1 and furin [37–44]. In the later section, we would see that ACE2 gene is regulated by epigenetic modifications.

3. A brief note on basic epigenetics: molecular mechanisms of gene regulation

"Epigenetics is the study of molecular mechanisms associated with regulation of chromatin dynamics which controls gene expression pattern in eukaryotic organisms without altering the DNA sequences of respective genomes" [45–47]. Epigenetics enables identical genomes to be expressed in numerous variations, thus it enables cell type and tissue specific as well as context dependent gene expression. A gene is expressed either constitutively or it is expressed in a context specific manner in response to external or physiological signals. The translation of a signal into a gene expression response could occur by different mechanisms. Following exposure to a virus like SARS-CoV-2, binding of the virion to the cell membrane by a receptor protein changes conformation of the membrane protein, the local organisation of the membrane will be perturbed and the actin/tubulin/filament cytoskeleton will sense it, as a result, a mechanical signal may transduce through 'linker of nucleoskeleton and cytoskeleton' (LINC) complexes to the nucleus to alter gene expression [48].

The chromatin is composed of DNA and four types of histone proteins (H2A, H2B, H3 and H4). The smallest unit of chromatin is the nucleosome and nucleosomes are comprised of histone octamer (formed by two molecules of each histone) wrapped 1.7 times by DNA of 146 nucleotides long and linked by DNA sequence, known as linker DNA [49,50]. Another type of histone i.e., H1 remains associated with the linker DNA and is thus known as linker histone [51,52]. During the formation of nucleosome, $(H3\text{-}H4)_2$ tetramer is formed first and DNA wraps it, thereafter (H2A-H2B)2 is deposited on to it. Due to the presence of phosphate groups DNA is negatively charged; accordingly evolutionary histone proteins have more positively charged amino acids. These negative and positive charges attract DNA and histones to each other and make a stable complex, thereby forming beads on a string organisation [53–55]. Reversible chemical (methyl-, acetyl-, phosphoryl-, dopaminyl-, ubiquityl- etc.) modifications at respective side chains of amino acids; lysine (K), serine (S), threonine (T), tyrosine (Y), arginine (R) and glutamine (Q) of nuclear histones impact gene expression and cellular functions. Among these, K undergoes versatile modifications, including methylation, acetylation, sumoylation and ubiquitylation; S, T and Y undergo phosphorylation; R undergoes mono- as well as symmetric/asymmetric dimethylation; Q undergoes methylation, serotonylation and dopaminylations ([20,35,56–61], reviewed in [62]).

To perform cellular functions utilizing DNA as template, DNA should be accessible, and this could be brought about by incorporation of methyl, acetyl etc. groups in the respective positively charged amino acids side chains of histones [56–63] thereby allowing DNA polymerase, RNA polymerase etc. to bind DNA for respective replication, repair or transcription.

In addition to histone modifications, covalent modifications of any of the DNA bases would occur by post-replicative enzymatic transfer of a methyl group to a base in DNA affect chromatin conformation. Cytosine methylation at the fifth carbon position (hereafter, DNA-methylation) occur in vertebrate genomes when it is found in the context of -CpG-dinucleotide sequence. CpG methylation in gene promoters, enhancers and other genome regulatory positions can transcriptionally inactivate a gene [64–71]. The enzymes involved in this process of gene inactivation are DNA methyltransferases (DNMTs; DNMT1, DNMT3A and DNMT3B) and histone deacetylases [69–74].

Epigenetic modulations are responsive to different signals that are derived from changes in metabolism [75], the environment [76], developmental processes [77] and are dependent as well on the DNA sequence context [69,78]. It stands to reason that the course of COVID-19 infection and its clinical consequences of infection are dependent on the underlying inter-individual variations in epigenetic programming of the host immune system and the target tissue as well as the epigenetic responsivity of the host immune and targets cells to COVID-19 infection. How could variations in epigenetic profile of the host immune and target tissues determine the clinical course of the response to COVID-19?

3.1. Modulation of epigenetic landscape of the host in viral diseases

In recent time series of reviews elaborated how the host-pathogen interactions are influenced by epigenetic modulations [79–87]. DNA and RNA viruses, both types, are involved in tumor development and cancer progression. Some of the well-studied DNA viruses are; Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human papillomaviruses (HPV) and hepatitis B virus (HBV). Among the RNA viruses two notable examples are human T-cell lymphotropic virus 1 (HTLV-1) and hepatitis C virus (HCV). 95 % of cervical cancers are caused by the DNA virus HPV. 80 % of hepatocellular carcinomas (HCCs) are associated with human HBV and HCV [2]. It has been deciphered that viral protein(s) interact with epigenetic factors and thus alter the epigenetic landscape of the host genome (for a recent review, see Poreba et al., 2011; ref., [88]). For examples, latent membrane protein 1 (LMP1) and 2A (LMP2A) of EBV activates DNMT1, DNMT3A and DNMT3B [81,88–92]; E7 of HPV binds and activates DNMT1 [80,93], interacts with HDACs [80,94]. The Tax protein of the retrovirus HTLV-1 is predominantly nuclear and interacts with cellular histone acetyltransferases CBP/p300 [95,96] as well as with BRG1 subunit of multiple chromatin remodeling complexes [97–99].

Epigenetic modulations impact the host immune response against infection for recovery from diseases [100], including COVID-19 [101–103].

Most of the (+ve) strand RNA viruses don't integrate with host genetic sequence (exception, for example, HIV); however, they may alter the host epigenome [104]. Several studies have implicated how viruses might disrupt the epigenetic network supposed to combine with H3K4me3 active marks in initiation of transcription of antiviral genes; as a result their expression is blocked. For example, Marazzi et al. have demonstrated that the carboxy-terminus of the H3N2 non-structural protein NS1 possesses sequence similarity with histone H3 N-terminal tail [105]; as a result, histone modification factors, enzymes like H3K4 methyltransferases (MLL family enzymes) H3K9 acetyltransferases may bind to NS1 instead of histone.

Clear association of repressive histone modification H3K27me3 and down-regulation of interferon (IFN)-stimulated genes after Middle East Respiratory Syndrome Corona Virus (MERS-CoV) and influenza viruses A/influenza/Vietnam/1203/2004 (H5N1-VN1203) infection are reported [106]. Similar studies are lacking in COVID-19. DNA methylation plays a similar role in the loss of antigen-presentation molecules following MERS-CoV and H5N1-VN1203 infection. Immune response of the host to H5N1 infection was prevented by histone methylation in cooperation with the viral protein NS1 and DNA methylation mediated repression of responsible genes involved in antigen presentation [107].

It needs to be determined whether COVID 19 alters chromatin modification similar to HIV-1 and herpes viruses [108,109]. There are lack of evidences in understanding the mechanisms, how HSV-1 infection downregulate the type I interferon (IFN). IFNs mediate cellular antiviral response and initiate pathogen-driven immune response by the inactivation of IFN stimulated genes (ISG) [110,111], and other viruses might also develop antagonistic mechanisms to overcome specific ISG effectors [112]. The epigenetic modulations are operated by enzymes and execute dual responsibility; firstly priming of memory and then executing operational pathways. The histone mark, H3K9me2 is a

repressive signal and help heterochromatin formation in correlation with the DNA methylation. H3K9 acetylation (H3K9ac) is strong expressive signal and H3K9me1/2/3 marks prevent acetylation; precisely, H3K9me2 have stronger affinity with heterochromatin protein 1 family [113]. That the H3K9me2 is an IFN responsive modification was correlated by the observation that the overall levels of H3K9me2 mark in the promoter region of the type I IFN gene and consequent down regulation of ISGs in dendritic cells [113,114].

Histone 3-Lysine 4 trimethylation (H3K4me3) precisely accumulate in gene promoters, including Toll-like receptors (TLRs) genes. During lipopolysaccharide (LPS) stimulation of macrophages and dendritic cells, there was increase of histone acetylation and enhanced binding of polymerase II (Pol II) to specific ISG genes promoters [115]. During H1N1 and SARS-CoV infection there was H3K4me1 accumulation and H3K27me3 depletion [100]; H3K4me1 generally precipitate in active enhancers facilitating transcription [13,102]. On the contrary, in MERS-CoV infected cells there was enhanced accumulation of H3K27me3 and depletion of H3K4me3 levels at the promoter region of ISGs subsets [106].

RNA modifications of SARS-CoV-1; for example, N6-methyladenosine (m6A) and N6,2′-*O*-dimethyladenosine (m6Am) modifications (m6A/m) are indispensable in the viral life cycle. RNA methylation at m6A [21–25] is the most abundant epitranscriptomic modification of eukaryotic mRNAs and essential for mRNA stability and guiding translation of the respective cellular and viral proteins [116,117]. m6A and its associated machinery regulate the DNA virus hepatitis B (HBV) life cycle, finalized through an RNA intermediate, termed pregenomic RNA (pgRNA) [118]. A specific m6A site in the 5′ epsilon stem loop of pgRNA guides the efficient reverse transcription of pgRNA.

In Kaposi's sarcoma-associated herpesvirus (KSHV) latent and lytic infection; KSHV transcripts are characterized by a high level of m6A/m modifications established during latent and lytic replication [119]. After the modifications reader protein binds m6A site. The reader proteins contain a conserved YT521-B homology (YTH) domain. In an assay of YTH N6-methyladenosine RNA binding protein 2 (YTHDF2) knock-down, it was found that KSHV RNA degradation is impaired. This suggests that YTHDF2 binds to viral transcripts and differentially mediates their stability [119]. There is specific 5mC methylation signature in coronavirus, SARS-CoV-1 RNA, which suggest that methylation of coronavirus RNAs is sequence-specific or controlled by RNA structural elements [120].

4. Intermediary metabolites and epigenetic mechanisms

Gene expression/repression is guided by epigenetic modifications of chromatin in response to respective signaling for maintenance of systems physiology and homeostasis [54–61,121–124]. The chemical/catalytic activity of most of the enzymes engaged in chromatin modifications depend on various cofactors, including acetyl-CoA as the donor of acetyl group in acetylation reactions. S-Adenosylmethionine (AdoMet or SAM) is the ubiquitous donor of methyl group in all methylation reactions, including synthesis of nucleic acids, phospholipids, creatine, polyamines and methylation of many bioactive molecules. ATP as the donor of phosphate group in reactions catalysed by kinases and others like NAD+, FAD and UDP are intermediary metabolites. For a detail discussion on the synthesis and involvement in respective reactions of these metabolites refer to [75], and also the recent review article by Etchegaray and Mostoslavsky, 2016 [125]. For a detail understanding consider the metabolism of the amino acid methionine, and the cofactor SAM. Methionine is an essential amino acid and when it reacts with ATP form SAM and the reaction is catalysed by the enzyme methionine adenosyltransferase (MAT; Fig. 2). Mammalian MAT [EC 2.5.1.6] is encoded by two genes MAT1A and MAT2A which display a tissue–specific expression pattern [126–129].

During severe infection in the lung, oxidative stress is induced. It is hypothesized that the systemic hypoxia may be due to local hyperoxia within cells of lung tissues for increased synthesis of RNA and protein for virus replication and for energy metabolism, growth arrest, and antioxidant defense. A study of SAM and methionine metabolism in lung epithelial cells A549 and primary small airway epithelial (SAE) cells implicated the increase of methionine metabolism and SAM content in response to hyperoxia. They analysed the expression of a MAT2A isoform containing a silent mutation in lung epithelial cell during hyperoxia, where MAT2A protein progressively increased in both transformed and primary lung epithelium [127]. While the liver specific MAT1A

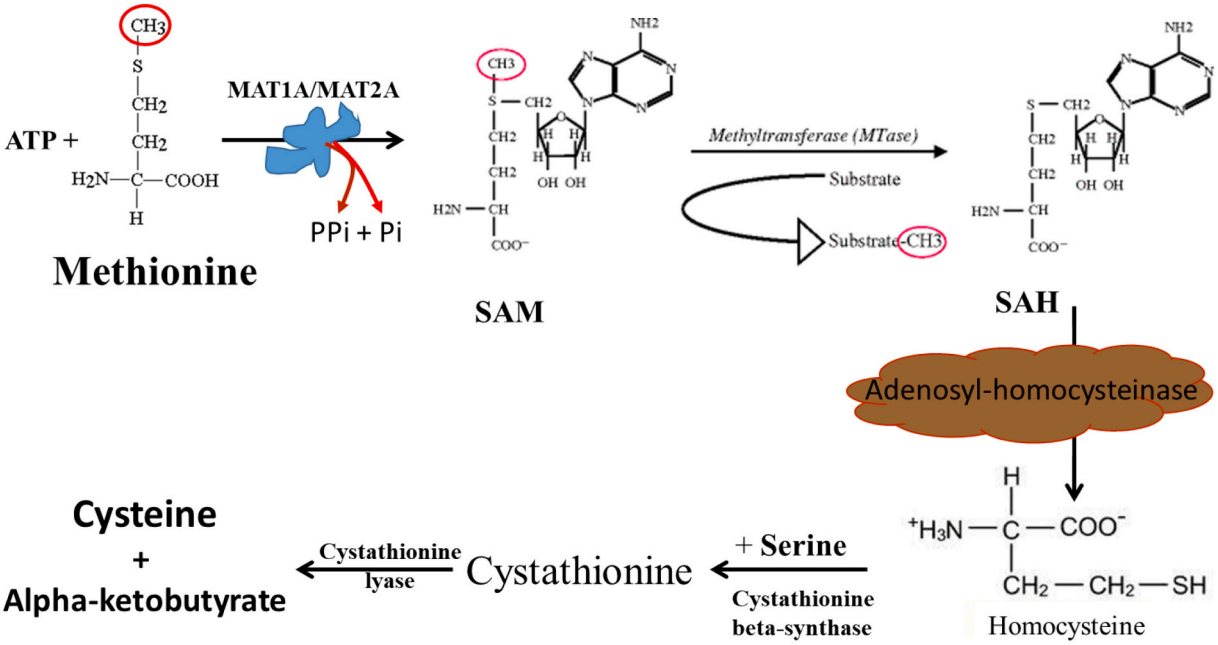

Fig. 2. Metabolism of the amino acid methionine. The cofactor S-Adenosylmethionine (SAM) is formed by the reactions of methionine with ATP with the release of Pi and PPi. SAM donates the $-CH_3$ group in all types of methyl transfer reactions, including DNA and histone methylations modulating gene expression. As a by-product SAH is produced, following three further steps cysteine is produced. [Amino acids and SAM structures are taken from Google].

gene is regulated by promoter methylation and histone deacetylation [128] and miRNA modulation of MAT1A expressions in relation to hepatocellular carcinoma are reported [129], similar studies with MAT2A gene in lung tissues and their relevance with SARS-CoV, MERS-CoV and SARS-CoV-2 infections are lacking.

Methionine is essential also for synthesis of cysteine by transsulfuration pathway (Fig. 2). Cysteine is the important component of glutathione, an antioxidant that prevents damage to integral cellular components caused by reactive oxygen species, including free radicals, peroxides, and heavy metals [130–134].

5. Epigenetics at the entry point: regulation of the angiotensin converting enzyme 2

ACE2 expression may be controlled by epigenetic pathways; and histone methyltransferase EZH2 (Enhancer of Zeste Homolog 2) mediated trimethylation of histone 3 lysine 27 (H3K27me3) modifications of ACE2 promoter could be a target for prevention and adjuvant therapy of COVID-19 [135]. DNA methylation of ACE2 gene promotor –CpG- sites is age and gender specific [136–138]. The extent of methylation is lowest in lung epithelial cells and highest in neurons and leukocytes [139]. Consistent with genome wide aberrant methylation in ageing [140], ACE2 gene remains demethylated and express highly in male [139]. In children the ACE2 gene remains partially silenced due to aberrant hypermethylation [141]. In comparison to control individuals ACE2 expression in COVID-19 patients with comorbidities is very high [136]. It is well documented that H3K27me3 deposition represses many gene in concert with H3K9me3 and DNA methylation [142,143], and H3K27me3 and H3K4me3 bivalent signatures poise genes during development [144,145]. ACE2 is a carboxymonopeptidase, an enzyme essential for renin-angiotensin system [146,147]. ACE2 generates angiotensin[1–9] peptides by hydrolysis of angiotensin I, the inactive precursor of angiotensin II. Angiotensin[1–9] further processed to the vasodilator peptide angiotensin[1–7] by ACE. ACE2 also directly acts upon angiotensin II to generate angiotensin[1–7]. Angiotensin[1–7] is well established as an important regulator of cardiovascular function, promoting vasodilatation, apoptosis and senescence.

In the context of COVID-19 and considering the importance and vastness of ACE2 function in system physiology, including in cardiovascular and renal activities [144,145], application of ACE2 blockers/inhibitors is not useful. Additionally, clinical complications by the use of ACE2 inhibitors to cure COVID-19 are very risky [148–150].

6. Regulation of TMPRSS2 by epigenetic mechanism

There are previous reports that TMPRSS2 enhance the infection of SARS-CoV and MERS-CoV and a recent report demonstrated that SARS-CoV-2 infection is also triggered by TMPRSS2 [151,152]. Proteolytic cleavage of ACE2 receptor by TMPRSS2 promotes viral uptake, and cleavage of coronavirus spike glycoproteins activates host cell entry. Tissues with large populations of epithelial cells generally express TMPRSS2 and transcription profile implicates highest level of expression in the prostate gland. Protein level expression is very high in lung type II pneumocytes and small intestine and also detected in colon, stomach and salivary gland [153]. It is coexpressed with ACE2 in lung type II pneumocytes, ileal absorptive enterocytes, intestinal epithelial cells, cornea, gallbladder and nasal goblet secretory cells [154]. TMPRSS2 activates many downstream factors of androgen signaling pathway, including pro-hepatocyte growth factor/HGF, the protease activated receptor-2/F2RL1, which disrupt extracellular matrix and thus enhance prostate cancer metastasis [155]. TMPRSS2 promotes prostate cancer by fusing with transcription factor ETS (Erythroblast transformation specific or E26 transformation specific) [156] and most of the studies on epigenetic regulation of TMPRSS2 gene appear from the perspective of prostate cancer [157,158]. A study in TMPRSS2–ERG fusion-positive (FUS+) and FUS− prostate tissues deciphered that DNA methylation pattern differs significantly with enhanced methylation in FUS− tumors. FUS+ samples exhibited DNA methylation patterns of specific genes modulated by epigenetic regulation are pretty similar to that of matched normal prostate tissues [147]. Years back we reported that DNA methyltransferases DNMT1, DNMT3A, DNMT3B and histone deacetylases HDAC1 and HDAC2 are over expressed in prostate cancer [159,160]. Recently we have shown that DNMT1 gene expression is silenced by micro RNA, miR148a over expression, while the latter gene remains silenced by DNMT1 mediated DNA methylation [161]. EZH2 trimethylates H3K27 and deposition of H3K27me3 represses miR26a gene [147]. EZH2 is overexpressed in recurrent nasopharyngeal carcinoma and miR26a play a crucial role [162] in progression of cancer.

7. Epigenetics of ribosome biogenesis and autophagy in viral infection

In a matured cell at steady-state total abundance of ribosome may reflect the biosynthesis of the complex as well as its turnover rates. Approximately, ~ 200 protein and RNAs are involved in biogenesis of ribosome [30,163]. About 60 % of transcriptional output remains engaged in the production of rRNA along with 50 % of RNA polymerase II transcripts and 90 % of splicing activity is engaged in ribosomes biogenesis. Metabolic labelling and kinetic data suggest that on an average a mammalian cell produce ~4000 ribosomes per minute [30], average size of the ribosomal proteins is 21.5 kD [129]. Abundance of ribosomes in a cell is well control by autophagy [164] and ubiquitin proteasome system [30]. Coronavirus induce *endo*-membrane rearrangements and autophagy. Viral infection in general [165] and coronaviruses in particular control autophagy [166,167] and exploit ubiquitin-proteasome degraded product during their replication [168–170]; however, the extent of ribosome turnover rates are not studied as of yet. Autophagy, including ribophagy and mitophagy plays crucial roles for maintenance of healthy lives [171,172]. That the production of rRNA is well controlled by epigenetic mechanisms is established [33,173], and the epigenetic regulation of autophagy is emerging [172,174].

8. The cytokine pathways are precisely linked with DNA methylation

The hallmark of chronic inflammation [175], stress or a viral infection is manifested by the response of the affected tissue, organ or the infected cell. Precisely, for viral infection there are antiviral defense machineries, including autophagy, apoptosis, and production of specific cytokines. Viruses like, HCV and HIV attacks the CD8 + T cells destroying its power to negotiate with the antigens [176–178]. Recent laboratory test and pathological data on COVID-19 patients evidenced a surge of cytokine expression, widely known as “cytokine storm” [179–181]. Among the cytokines, expression of interleukin 6 (IL-6) is of highest measure [182]. DNA methylation of IL-6 promoter represses the IL-6 gene expression in lung cancer [183]. There is a feedback loop between IL-6 and DNA methyltransferases (DNMTs). Overproduction of IL-6 differentially affects the stability of DNMTs [184]. This could be due to the overexpression of ubiquitin-proteasome components by IL-6 and DNMT1 ubiquitination is one of the major causes of its proteasomal degradation [185]. In other tissue system; as studied in intestinal epithelial cells by treatment with IL-1β, it was observed that various other cytokines are repressed by DNA methylation [186]. These suggest that there is a strong correlation between interleukin signaling and DNA methylation in both lung and intestine tissues and interestingly, ACE2 expression is high in these tissues [187].

Higher expression of interferon genes are commonly observed in systemic lupus erythematous (Syluer) and characterized by a cytokine storm [188], and a cytokine storm is characteristic of SARS-CoV-2 [189–191]. Syluer patients prevail with COVID-19 comorbidities, as observed in cases of lung diseases, chronic kidney disease and obesity

[189]. Epigenetic data and comorbidity analyses implicate that Syluer patients are more susceptible to SARS-CoV-2 may not be due to loss of immunity; however, due to the presence of higher amount ACE2 protein as a result of hypomethylation of ACE2 gene as well as interferon genes [190].

9. Epigenetic modulators that may be used as supplement with antivirals against COVID-19

Detailed understanding of tissue specific epigenome is in progress and it differs widely from disease to disease. Accordingly, the epigenetic profile of cancerous lung cells differs widely from COVID-19 lung cells. Investigations whether the non-structural proteins and proteins coding by ORF6/7/8 of SARS-CoV-2 interact with epigenetic enzymes would be very useful to develop epigenetic drugs against COVID-19. As presented in previous sections, the major target genes would be ACE2, TMPRSS2 and furin to prevent entry of the virus and various cytokines. We don't know the exact mechanism/pathway by which SARS-CoV-2 endocytosed; however, involvement of lipid rafts is implicated [191]. Epigenetic modifiers from natural resources (for example, from medicinal plants) would be the best medicine. In vitro data suggest that use of vitamin D and quercetin would ameliorate COVID-19 severity by inhibiting the expression of ACE2 and furin [192,193]. Curcumin and 8-hydroxyquinolones may silence ACE2 and interferon genes by activation of DNMTs within viable clinical doses [194–196]. Among the notable drugs those can modulate DNA methylation and histone acetylation capacities are sulforaphane [197] and thymoquinone [198] that inhibit HDAC, lupeol and β-sitosterol from P. fotida plant extract that repress DNMTs, IL-6, IL1-β, TNF-α [199], and procyanidin B2 inhibits DNMTs [200].

A few antiviral drugs went on or under trials and/or in use under compassionate grounds are listed in Table 1. These drugs are not specific against SARS-CoV viruses; yet Remdesivir is effective. Among the others, Favipiravir, Umifenovir or Lopinavir/Ritonavir alone or in combination with antimalarial drug chloroquine/hydroxychloroquine or along with interferon beta-1b and ribavirin reported to be effective; Convalescent plasma, mesenchymal stem cell derived exosomes, Chinese traditional medicines and supplementation with Vitamins C and D are widely in use [4–6,201–209].

FDA approved compounds targeting epigenetic modifiers/enzymes in combination with antiviral drugs would be very useful and beneficial against viral replication, modulation of the host immune response, and hence, better management of the disease [209]. Metabolic aspects including pharmacokinetic and pharmacodynamic properties of antivirals may also be modulated by epigenetic mechanisms; for example, by alteration of the expression of drug uptake/efflux pumps. Hence, it is relevant to use small molecule/chemical modifiers of epigenetic marks for the treatment COVID-19 [209,210]. Non-structural proteins (nsps), involved in viral transcription, replication, and maturation processes of human cytomegalovirus (HCMV) and HIV infections are evidenced to be regulated by HDACs. Thus, HDAC inhibitors, including suberanilohydroxamic acid (SAHA) and/or Vorinostat in combination with antivirals would be useful [211,212]. As has been mentioned elsewhere in this report, expression of ACE2 gene is down regulated by DNA methylation and histone modifications, including EZH2 mediated H3K27me3 deposition. Accordingly, epigenetic enzymes, DNMT1, EZH2, histone acetyltransferases (HAT), histone deacetylase 1/2 (HDAC1/2), and lysine demethylase 5B (KDM5B) are emerging targets for potentiation of immune response genes of the host [103,213]. Hence, inhibitors like Azacitidine against DNMT1, anacardic acid against HAT1 and valproic acid against HDAC1/2 would be applied in clinics to outfitting various diseases caused by corona viruses, including COVID-19 [204,214].

To repurpose epigenetic drugs, those are approved for use against cancer therapies; the nature of host epigenetic machineries exploited by the respective virus needs to be explored for their broad-spectrum antiviral action and inflammatory control [209,215]. 5-aza-2′-deoxycytidine (5-azadC) and/or decitabine, DNMT inhibitor(s) is/are frequently used for suppressing inflammation and IFN response by inhibition of DNA methylation in macrophages [209]. It would be very interesting to observe how decitabine impacts clinical trial for COVID-19 Pneumonia-ARDS Treatment (CTI: NCT04482621).

It is known that natural killer cells after a long-term boosting exhibit immune response by epigenetic mechanisms [216–218] and lung innate lymphoid cell group 2 also exhibit same mechanism. Receiving a primary stimulus these cells reprogram their metabolic and mitochondrial activities by epigenetic reprogramming, this sets a memory phenotype with enhanced immune responses after the exposition to a secondary stimulus [219].

RNA-based chemicals must be tested as alternative epigenetic compounds for treatment of disease caused by viral infections [220,221]. The 5′UTR region, essential for viral RNA replication and transcription of SARS-CoV-2 could be targeted to design novel antisense molecules [222]. Small interfering RNAs (siRNAs), microRNAs (miRNAs), and locked nucleic acid antisense oligonucleotides or GapmeRs, targeting, for instance, the 5′URT or regions of the Spike molecule, represent potential therapeutic tools for both prophylaxis and therapy of COVID-19 [222–227]. Advanced bioinformatic tools are emerging to decipher and interpret the global epigenomic data in silico. This in silico data with experimental validation explains genetic status and epigenetic manipulations from the affected population. Thus we may acquire large data sets to understand how the environmental changes in the host cell modulate the function of our genes by imposing long-term marking on the epi-genome.

Information from mice models fall short for many marked differences between the human and mice brains, lungs, liver etc. in sizes and functions. For example, differences in brains including structure (gyrencephalic vs lissencephalic); size (1000-times larger with 10-times more neurons in humans); types and number of stem/progenitor cells and the time taken for developing the entire central nervous system (approx. 34 weeks in human vs 11 days in mice). With the deficit in information regarding the mode of infection and disease development

Table 1
List of drugs used against COVID-19.

Drugs	Originally developed against (target)	Reference ClinicalTrials.gov Identifier (CTI)	Efficiency against SARS-CoV-2 (References)	Mode of action
Remdesivir	RDRP/Ebola	NCT04431453	High (CTI, 6, 2005, 2006)	Impairs replication
Lopinavir/Ritonavir	MPro/Ebola	NCT04386876	Medium/low (CTI, 4, 5, 205–207)	Impairs processing of nsps
Ribavirin	RDRP/HCV	NCT01097395	Low (CTI, 4–6, 204)	Interfere replication
Oseltamivir	Neuraminidase/Influenza	NCT02507648	Weak (CTI)	Impairs spreading of virus
Favipiravir	RDRP/Influenza	NCT04336904	Weak (CTI)	Interfere replication
Umifenovir	Impairs host-virus interaction/ Broad spectrum	NCT04476719	Weak (CTI)	Impairs trimerization of Spike protein
Azithromycin/Oseltamivir/ Hydroxychloroquine	Broad spectrum/Neuraminidase/ Antimalarial	NCT04338698	Medium (CTI)	Impairs virus encapsulation

aspects or the exact mechanism of regulation, therapeutics developed in mice models of varied diseases; for examples, Alzheimer's, Parkinson, Huntington, fragile X syndrome do not work efficiently in human as the etiology of disease is different and the phenotypic manifestation doesn't match to the abnormalities observed in humans.

10. Discussion and perspectives

There are need for more research on the metabolic and epigenetics aspects of ss(+)RNA virus infection and disease progression to clearly understand the pathophysiology. Current research data have highlighted that the lung utilizes metabolic energy equivalent to liver, kidney and brain [38]. The house keeping functions, including cytoskeleton rearrangements, maintenance and repair of DNA damage, gene expression and protein translocation are at high rate as lung cells constantly negotiates with external environment during O2/CO2 exchange. Specialized functions, including phagocytosis and ciliary motility, secretion in bronchial gland, constriction and amplification of airways and blood vessels, and synthesis of pulmonary surfactants are highly energy-consuming processes [38,228,229].

Environmental impact on the epigenome [76,78,123] and roles of DNA methylation in CpG-related mutations are emerging [230,231]. COVID-19, the disease caused by the SARS-CoV-2 virus infection is affecting our lives in all the ways. Careful scrutiny of the host-virus interactions from entry, replication, packaging and egress suggest that epigenetic alterations are involved within the host components only. Evidences are accumulating that 'cytokine storm', due to over-expression and activity of soluble markers of inflammation is the main culprit for the deaths due to COVID-19. There are several important genes, including ACE2, rDNA and IL-6 those could be epigenetically engineered for prevention of coronavirus spreading to other organs and transmission to other host. The data available as of today on the epigenetic investigations SARS-CoV-2 infection are very little. Regarding optimisation of production of vaccines scientists are working very passionately [232–235]. Synthesis of antibody not only depends on the nature of antigens, but on the cellular metabolic status and epigenetic influences and signaling pathways that affects reactions involved in epigenetic modifications. Hence, there is ample scope for epigenetic intervention of COVID-19. We hope to see the clinical and experimental data employing FDA approved epigenetic drugs along with antivirals. Some products leading to become effective vaccine(s) are on the pipeline and various national regulatory authorities are reviewing some COVID-19 vaccines (see the links; [236,237]), and one product from Pfizer has already been approved in certain countries. Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) already announced that, their mRNA-based COVID-19 vaccine candidate, BNT162b2, met all of the study's primary efficacy endpoints (see the link; [238]).

Aberrant signaling and modulation of epigenetic landscape are responsible for differential expression of genes in multiple diseases, including cancer, and we are working on this area for the last twenty three years (SKP) and well over thirty five years (MS). Epigenetic mechanisms of viral diseases are not explored adequately for risk factors in humans and lack of proper model systems that represent the human organs those are of primary targets of respective viruses. We suggest well designed experimental evidences and analyses of epigenetic landscapes against SARS-CoV-2 infection to better understand COVID-19 progression and to design best therapeutic measures.

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Author contributions

SKP conceived the project, SKP and MS planned the draft proposal, SKP drafted the manuscript, MS edited and corrected the English language, SKP and MS revised and approved the final version of the manuscript.

Declaration of competing interest

We declare that there is no conflict of interest.

Data availability

Data will be made available on request.

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