

Significance of Epigenetics in Sars-CoV-2 Infection and Proposed Epi-Drugs for Covid-19

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ABSTRACT

We frequently come in contact with animal viruses through the food which we eat, the pets which we have, and our connections with nature. The enormous majority of viruses which enter our bodies pass inoffensively through our physiological systems or eradicate by our immune systems. However, on rare circumstances, a human-encounters by a virus which begins to replicate itself, accomplishing its entire lifecycle within human cells and intensifying themselves into a large number. Replication of an animal virus inside the human body is the key instant in the zoonotic process. SARS CoV-2 is one of these viruses which cause COVID-19 disease. To enter the target cell SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2). Genome stability and maintenance of cellular equilibrium are the main parameters influenced by epigenetically regulated chromatin structure. Implication of regulation by epigenetic machinery has also been found in the physiopathology of the virus infection. By varying the function of gene locus. such regulation links genotype and phenotype without changing the original DNA sequences. However antiviral drugs have been used to treat various viral diseases since long, epi-drugs are now proposed to treat these diseases due to the epigenetic implications found in these infections. Epi-drugs are small agents that are able to reverse some epigenetic changes. This review is aimed to find implication of epigenetics in infection caused due SARS CoV-2 and if there is any epi-drugs approach possible to treat this infection.

Key Words: ACE2, Epi-drugs, Epigenetics, SARS CoV-2.

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INTRODUCTION

In January, it has been found that a novel coronavirus 2019-nCoV now named as SARS-CoV-2 is the causative agent of the disease named as COVID-19 (for "coronavirus disease 2019"). Human coronaviruses were 1st identified in the mid-1960s. The human coronaviruses (HCoVs) are from two genera: alpha coronaviruses (HCoV-229E and HCoV-NL63) and beta coronaviruses (HCoV-HKU1, HCoV-OC43), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and the severe acute respiratory syndrome coronavirus (SARS-CoV). Majority of the viruses from corona virus family are capable to alter the host epigenome while incompetent of hacking the gene sequence of the host (Atlante et al., 2020). Coronaviruses such as HCoV-NL63, SARS-CoV, and SARS-CoV-2 having angiotensin-converting enzyme

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2 (ACE2) as their receptor on the host cell which is also associated with the maintenance of the blood pressure and renin-angiotensin system (Beacon et al., 2020). Angiotensin-converting enzyme 2 can play a protective role in lung injury, and its downregulation by SARS-CoV aids in progression

to severe lung injury (Crimi et al., 2020). ACE2 is majorly found to be considerably expressed in the lower respiratory tract such as type II alveolar cells (AT2) of the lungs, upper oesophagus and also in kidney proximal tubule cells, bladder urothelial cells, absorptive enterocytes, cardiomyocytes, and cholangiocytes.

Several findings of the host genes and pathways that mediate pathogenesis of CoVs are the source that help us to understand the causal mechanism of the disease by these viruses, the reason behind the variation in the susceptibility of host may reveal host-directed therapeutic targets against known and unknown CoVs (Wei et al., 2020).

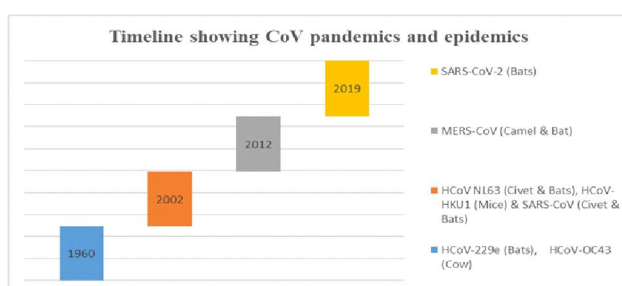


Figure 1: Timeline of CoV Pandemics and epidemics along with their host from which they are originated

Genetic and epigenetic variations in ACE2, TMPRSS2 and FURIN genes, act as central components for SARS-CoV-2 cell entry (Ragia and Manolopoulos, 2020). Chemical modifications to DNA, histone, non-histone chromosomal proteins, and RNA are the key players in epigenetic control which establish a complex regulatory network that controls genome function (Beacon et al., 2020). Several studies states that SARS-CoV-2 induces epigenetic changes of DNA methylation, that affects expression of immune response genes and could in part contribute to COVID-19 pathogenesis (Li et al., 2020). It has been reported that oxidative stress induced by SARS-CoV-2 infection is responsible for hypomethylation of ACE2 on the X chromosome which results in overexpression of ACE2 (Patra et al., 2020; Pruimboom, 2020). Through epigenetic mechanisms especially CpG methylation viral infections induce enterocytosis and syncytium development (Pruimboom, 2020).

Several potential epigenetic regulators of ACE2 in the lungs of human, containing genes involved in modifications of histone, such as HAT1, HDAC2 (histone deacetylase 2) and KDM5B are proposed with the Systems biology approaches on transcriptome samples from COVID-19 patients (Ragia and Manolopoulos, 2020).

Expression of proinflammatory cytokines, such as IL-6, IL-1, IFN- γ , IL-18, & TNF- α in host might get altered through interference of its epigenetic machinery by SARS CoV-2 (Atlante et al., 2020).

As few epigenetic changes can be reversed by small agents, called as 'epi-drugs', or alternatively, epigenetic pathways can be interfered by immune modulators, they might provide useful drug targets to ameliorate the clinical outcome during viral respiratory infections (Crimi et al., 2020). Clinically trailed epigenetic therapies, accepted epigenetic-targeted agents and antivirals-epi-drug combination treatment are now observed as an effective approach for viral replication and inflammatory overdrive control (Baba and Herbein, 2020).

COVID-19 AND EPIGENETIC REGULATION OF ACE2 EXPRESSION: THE GATEWAY OF SARS-CoV-2 INFECTION

DNA methylation of ACE2 gene and post-translational changes in histones are varying among host tissues, biological age and sex patterns which might be responsible for the pathophysiological differences of SARS-CoV-2 infections (Choudhary et al., 2020; Corley and Ndhlovu, 2020); FREITAS et al., 2020; Pruimboom, 2020).

DNA Methylation and ACE2 Expression

Current researches have reported that based on methylation pattern of several promoter CpG islands, there might be an association between the ACE2 gene expression with age and gender (Beacon et al., 2020; Pruimboom, 2020). ACE2 promoter hypomethylation may be one of the relevant drivers of COVID-19 (Choudhary et al., 2020; Crimi et al., 2020). Air pollution, cigarette smoke, and allergens are the environmental challenges which can directly enters the human body via nasal route where the ACE2 expression level is high and hence somehow

contributing towards SARS-CoV-2 infectivity and COVID-19 severity by modulating the epigenome of nasal epithelium than lungs. Among black males, hypomethylation of ACE2 could be the reason behind increased SARS-CoV-2 infection as abundance of ACE2 receptors are present in their nasal epithelium. This varying DNA methylation could be due to distinct social and environmental exposures (Cardenas et al., 2020).

Post-transcriptional ACE2 transcript levels are regulated by microRNAs (hsa-miR-125a-5p, miR-200 family) by targeting the 3' untranslated regions of ACE2 RNA. Reduction in expression of miR-125a and members of the miR-200 family are observed by demethylation of H3K4me3 by lysine demethylase KDM5B and hence KDM5B is somehow regulating the expression level of ACE2 transcript (Beacon et al., 2020).

Histone modulation and ACE2 Expression

Studies reported that histone modification (H3K4me1, H3K4me3, H3K27Ac) in ACE2 gene is associated with increased ACE2 expression and they have also mentioned upregulation of NAD-dependent histone deacetylase Sirtuin 1 (SIRT1) is associated with increased ACE2 expression (Choudhary et al., 2020). SIRT1 stands for silent information regulator T1a histone deacetylase class III binds to promoter of ACE2 and significantly regulate its levels (Baba and Herbein, 2020).

HDAC controls the expression of p300 and helicases such as Nsp13 are supposed to be controlled by p300. Viral replication also includes Nsp3-Nsp4-Nsp6 complex out of which Nsp4 interacts with HDAC2. Thereby from these findings this can be proposed that HDAC inhibitors might interfere with the replication of coronavirus which emphasize the role of epigenetic therapies in blocking HDAC2 (Baba and Herbein, 2020).

The main 3CLpro of coronavirus critical for the maturation of nsps i.e., non-structural proteins of SARS-CoV-2 is Nsp5. Cleavage of HDAC2 and tRNA methyl transferase 1 (TRMT1) results from their binding with 3C like protease (3CLpro) and hence expression of viral and/or cellular gene in infected cells might be aided by 3CLpro which act as HDAC2

inhibitor. As tRNA modifications catalysed by TRMT1 required for redox homeostasis, its cleavage by 3CLpro might lead to interference by SARS-CoV-2 with tRNA methylation in infected cells. Activity of 3CLpro reported to be inhibited by several drugs including the anti-HIV drug lopinavir (Baba and Herbein, 2020).

Wei et al., 2020 reported that HMGB1 controls ACE2 expression and hence indirectly contributing to the entry of SARS-CoV-2. HMGB1, a pleiotropic protein regulates chromatin by binding with nucleosomes in the nucleus, acts as a guard of non-self nucleic acids and transports genetic material, and functions as a secreted alarmin in response to virus infection (Andersson et al., 2020; Simpson et al., 2020; Wei et al., 2020). Their findings demonstrate that HMGB1 regulates expression of ACE2 in a cell-intrinsic manner and not via its role as a cytokine or alarmin, suggesting a distinct mechanism of HMGB1 in SARS-CoV-2 infection.

Epigenetic implications on Expression levels of CYP450 variants responsible for HCQ metabolism

Cytochrome P450 is a key modulator in the metabolism of (HCQ) hydroxychloroquine. Several findings state that HCQ has a higher safety and anti-viral activity to fight against SARS-CoV-2 infection. Post-transcriptionally, the expression levels of numerous CYP genes are affected by ncRNAs, for example by miRNAs and lncRNAs, and hence influence the metabolism, and bioavailability of drugs mediated CYP450. By modulating the expression of CYPs, methylation of DNA and acetylation on histone might be involved in the regulation of CYP-metabolized drugs (Paniri et al., 2020).

EPIGENETICS AND PROPOSED TREATMENT FOR COVID-19

Epi-drug to treat SARS-CoV-2

Some natural compounds that may induce epigenetic silencing of ACE2 gene include the deferasirox, DNA methyltransferase inhibitor curcumin, 8-hydroxyquinolones (8HQ) exhibiting a preventive potential towards SARS-CoV-2 infection (Chlamydas et al., 2020; Pruimboom, 2020). Sulforaphane is another epi-drug found to have methylation capacity. These substances help in

reduction of disease severity and susceptibility. Increased ferritin levels found in COVID-19 patients significantly worsen the outcome and an epi-drug Curcumin is found to have ferritin-lowering effects (Pruimboom, 2020). SARS CoV-2 found to be potentially inhibited by epi-drugs such as HDAC inhibitors, DNMT1 inhibitors, & BRD4 inhibitors, (Baba and Herbein, 2020; Gordon et al., 2020).

Table- 1: Proposed Epi-drugs for SARS-CoV-2

Chemical Compound	Epigenetic-related effects	Reference
Apabetalone	Possible reduction of viral infection and replication	Crimi et al., 2020
Deferasirox	epigenetic silencing of ACE2 gene	Chlamydas et al., 2020; Pruimboom, 2020
Curcumin and sulforaphane	DNA methyltransferase inhibitor	Chlamydas et al., 2020;
8-hydroxyquinolones (8HQ)	DNA methyltransferase inhibitor	Pruimboom, 2020
Vitamin D and quercetin	Inhibition of ACE2 and furin expression	Pruimboom, 2020
Vitamin D	Act as DNA methyl transferase/histone deacetylase	Singh, 2020

Targeting lipid metabolism as a treatment for COVID-19

Alterations in lipid metabolism have been detected as far as 12 years from the initial infection in SARS-CoV patients. Experimentally at the cellular level metabolism of lipid has been proposed as a treatment target for COVID-19 while epidemiological associations between COVID-19 and lipid metabolism are currently not possible, since even large scale cohorts do not report on relevant measurements; specifically, both interactions between SARS CoVs spike protein with lipid rich membrane compartments, as well as the epigenetic modulations in lipid metabolism were considered as the end-point targets for the development of small molecules, aiming to prevent COVID-19 (Vavougiou, 2020).

Targeting Cytokine regulation as a treatment for COVID-19

Some findings indicated the cytokine storm as the main cause for the COVID-19 deaths, in which an uncontrolled and excess production of soluble markers of inflammation has been reported.

The polycomb repressive complex 2 (PRC2) can also be considered a significant target for the treatment which transcriptionally represses IFN-

stimulated genes through their H3K27me3 (Atlante et al., 2020).

Geller et al., 2020 also evaluate immune dysregulation and cytokine storm affected by α -glucan, observed in COVID-19. They observed that TRIM has driven by α -glucan. TRIM is a form of memory possessed by innate immune cells is a long-term boosting of innate immune response. Natural killer cells and lung native lymphoid cells group 2 are the cells which mainly maintains TRIM through epigenetic mechanism. Changes due to aforesaid mechanism pointing towards these cells as a target for COVID-19 treatment.

Proinflammatory cytokines and chemokines expression is favoured by demethylation of the IFN-regulated genes (viz. NF- κ B) and key cytokine genes which leads to increasing incidence of cytokine storm. Hence epigenetic control of ACE2 gene and reduction of plasma IL-6 concentration valour is goal for avoidance and treatment in COVID-19 (Baba and Herbein, 2020). IL-6 expression will get affected by the alteration in DNA methylation and histone acetylation states in its promoter (Chenet et al., 2020).

IL-6 levels are found to be inhibited by histone acetyltransferase inhibitors (HATi) such as anacardic acid, MG149, and C646. DNA methylation in macrophages is commonly inhibited by a nucleoside based DNMT inhibitor Decitabine which directs suppression of inflammation (Baba and Herbein, 2020). SARSCoV-2 infection in epithelial cells of the airway also shapes the immune landscape in the lungs of COVID-19 patients. Thus, the prominent epigenetic regulators such as HDAC2 and BRDs (BRD2, BRD4) communicate with Nsp5 and E viral proteins respectively. Inflammatory functions and IFN response induced by HDAC2 are affected by Nsp5 which resist the transportation of HDAC2 into the nucleus (Baba and Herbein, 2020; Gordon et al., 2020). Reduction of TNF α protein level results from the transcriptional repression of TNF α promoter through binding with H3K9 histone methyltransferase G9a which is directed by DNA methylase DNMT3a/b. Histone acetylation (H3K36ac, H4K5ac and H3K9ac,) suppress TNF α and IL-8 level, that be majorly produced in response to CoV. The production of these proinflammatory

mediators was curbed by way of wide band HDACi, TSA, (Baba and Herbein, 2020; Herbein and Wendling, 2010). The production of these proinflammatory mediators was curbed by way of wide band HDACi, TSA, (Baba and Herbein, 2020; Herbein and Wendling, 2010) and also three dimensional printing are helping a lot for simulation and modeling for early checking on replacing any failed organs and also role of engineering nanomaterials play a vital role in this work [26].

Targeting Histone deacetylases (HDACs) for the treatment of COVID-19

HDACs are recognized for regulating the transcriptional activity of targeted genes. They act by deacetylation of amino terminal lysine residues of histone and non-histone proteins. HDACs are also capable of epigenetic regulation of TGF- β -mediated gene expression (Murthy et al., 2020).

SIRT1 and resveratrol from histone deacetylase class III have been previously described as antiviral effectors. Resveratrol act as DNA methyltransferase (DNMT)1 and as an activator found to target the regulation of viral infection by modulating SIRT (SIRT 1,2,3,5) activity. Class II HDAC found to be inhibited with the use of approved drug valproic acid (VPA) as well as pre-clinical applicant apicidin (Gordon et al., 2020). Regardless of concentration, VPA shows minimal control on high cytotoxicity levels along with the growth of SARS-CoV-2 (Baba and Herbein, 2020).

CONCLUSION

Coronaviruses are infecting human across the globe since a long time. Somehow host epigenetic machinery has been reported to be involved in the infections triggered by these viruses. In our study we have compiled various studies reported the involvement of host epigenetic machinery during the SARS-CoV-2 infection. The studies we have reviewed were collected from the recent publication in the year 2020 on the PubMed database. ACE2 is the receptor for various coronaviruses including SARS-CoV-2 which act as the gateway for the virus to enter inside the host cells. The main mechanisms which epigenetically regulate ACE2 expression in the SARS-CoV-2 infection are DNA

methylation and histone modifications. Drugs targeting the molecules involved in the epigenetic regulation of the ACE2 are now proposed and clinically trail to treat pathophysiology of COVID-19 such as hyperinflammatory storm, which could make the epi-drugs therapy a major asset in restricting SARS-CoV-2 infection.

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