



The severity of SARS-CoV-2 infection is dictated by host factors? Epigenetic perspectives

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ABSTRACT

The emergence of COVID-19, caused by SARS-CoV-2 poses a significant threat to humans as it is highly contagious with increasing mortality. There exists a high degree of heterogeneity in the mortality rates of COVID-19 across the globe. There are multiple speculations on the varying degree of mortality. Still, all the clinical reports have indicated that preexisting chronic diseases like hypertension, diabetes, chronic obstructive pulmonary disease (COPD), kidney disorders, and cardiovascular diseases are associated with the increased risk for high mortality in SARS-CoV-2 infected patients. It is worth noting that host factors, mainly epigenetic factors could play a significant role in deciding the outcome of COVID-19 diseases. Over the recent years, it is evident that chronic diseases are developed due to altered epigenome that includes a selective loss/gain of DNA and histone methylation on the chromatin of the cells. Since, there is a high positive correlation between chronic diseases and elevated mortality due to SARS-CoV-2, in this review; we discuss the overall picture of the aberrant epigenome map in varying chronic ailments and its implications in COVID-19 disease severity and high mortality.

Introduction

SARS-CoV-2 has caused a staggering pandemic across the world, with a terrible consequence for well-being and economies. The Coronaviruses fall under single-stranded positive-sense RNA viruses of the *Coronaviridae* family, which exhibit zoonotic transmission. It has four genera; of which the alpha CoV and beta CoV affect only mammals, whereas the gamma CoV and delta CoV infects birds and mammals, including dolphins and whales (Cui et al., 2019; Ar Gouilh et al., 2018; Monchatre-Leroy et al., 2017). The previous outbreaks include the severe acute respiratory syndrome (SARS) caused by SARS-CoV-1 and the Middle East respiratory syndrome (MERS) caused by MERS-CoV (Dye C and Gay N, 2003; Drosten et al., 2003; Memish et al., 2013, 2014). The current episode of the SARS-CoV-2, known as coronavirus disease 2019 (COVID-19), was declared a pandemic by WHO creating an international emergency (Zhu et al., 2020; Gupta et al., 2020). The SARS-CoV-2 is shown to bind and infect the host cells by utilizing the membrane-bound Angiotensin-Converting Enzyme 2 (ACE2) receptor (Shang et al., 2020;

Letko et al., 2020). Upon binding to the receptor and viral entry, the replication is initiated with the help of viral replicases, which facilitate the RNA replication and capping and viral particle synthesis (di Wilde et al., 2018).

The lung airway cells, the upper respiratory epithelium, and surface of the lung alveolar epithelial cells exhibit increased expression of ACE2 receptor, the primary site of SARS-CoV-2 infection (Sungnak et al., 2020; Ziegler et al., 2020; Hamming et al., 2004). In addition, multiple human tissues, including the lung, pancreas, brain, gut, and blood cells, expresses the ACE2 receptor (Li et al., 2020; Jia et al., 2005; Hamming et al., 2004). The ACE2 gene is located on the X chromosome, which encodes a functional receptor for SARS-CoV-2 spike glycoprotein required for viral entry into epithelial cells (Culebras E and Hernandez F, 2020). When compared to all other tissues, lung epithelial cells had the lowest levels of DNA methylation, which explains the increased expression of ACE2 receptor in these tissues (MJ Corley and Ndhlov., 2020). Further, the study had identified that the DNA methylation varied on the ACE2 gene by tissue, cell type, gender, and age (MJ Corley

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and Ndhlovu, 2020). There were differences in the methylation of the 2 CpG sites on the ACE2 gene in the human lung tissues with gender. Whereas, the airway epithelial cells showed varied DNA methylation near to the transcriptional start sites (TSS) of ACE2 gene with ages. Further, in freshly isolated airway epithelial cells, the presence of aberrant DNA methylation near the transcription start site (TSS) of ACE2 gene (MJ Corley and Ndhlovu, 2020). The increased expression of ACE2 transcripts were identified in the epithelial cells of upper respiratory tract regions viz bronchi, larynx, nasal, respiratory sinuses, and tongue keratinocytes (Qi et al., 2020; Xu et al., 2020; Ziegler et al., 2020; Hou et al., 2020). It was also found that ACE2 expression was higher in nasal cells than distal lung epithelial cells (Hou et al., 2020). The presence of differential DNA methylation in the nasal epithelial cells are common among the children and it was also reported that presence of differential methylation on the 15 CpG sites on the ACE2 genes with respect to age, sex and race (Cardenas et al., 2021). It is evident that the high degree of variation of the DNA methylation signatures on the ACE2 gene promoter causes the differential ACE2 expression in the epithelial cell, which could be prime reason for the varying degree of infection among the different individuals.

The symptoms of COVID-19 typically appear between 2 – 14 days after the exposure to virus. The most common symptoms include fever, cough, and tiredness, and some cases loss of taste or smell (Guan et al., 2020; MJ Huang et al., 2020; Wang et al., 2020). The severity of COVID-19 symptoms vary among the infected individuals, some experiences severe symptoms, including shortness of breath and the development of pneumonia. Many infected individuals are recovered from the mild symptoms; however, still, the host factor that drive the development of severe COVID-19 remain unknown. The emerging reports have indicated that the severe disease develops in aged individuals with pre-existing chronic diseases like pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury (Guan et al., 2020; MJ Huang et al., 2020; Wang et al., 2020). However, the clinical symptoms of infected individual varies with emerging variants of SARS-CoV-2. The most virulent form of SARS-CoV-2 is a Delta variant (B.1.617.2), which was first identified in India in Dec. 2020 and within a short span of time, this variant spread across to nearly 98 countries (Rubin et al., 2021). The Delta variant is

account for nearly 83% of COVID19 cases. The SARS-CoV-2 delta variant is 50–60% highly transmissible than the originally identified Wuhan strain and moreover, it is reported that the infected patients airway epithelial cells are with high viral load (Lythgoe et al., 2021). The clinical symptoms of the SARS-CoV-2 Delta variant is little different than other strains, the Delta variant infected patients presented with fever, running nose, sore throat and headache are common, however these patients have minimal cough and there is no loss of smell which is very common with original SARS-CoV-2 strain (Frampton et al., 2021; Singh et al., 2021). In addition, the Delta variant has more severe symptoms including hearing impairment, severe gastrointestinal issues and blood clots leading to tissue death, which also account for increased hospitalizations (Frampton et al., 2021; Singh et al., 2021).

The main problem associated with SARS-CoV-2 is co-morbidity and increased risk to individuals having chronic diseases (Xia et al., 2020; Richardson et al., 2020). The host epigenetic factors like DNA and RNA methylations, post-translational modifications of histones, non-coding RNAs are essential for normal cellular development (Fig. 1). Aberrant epigenetic signaling that leads to defect in cellular development and is commonly reported in many chronic diseases (Benincasa et al., 2020; G. Chen et al., 2020; Mongelli et al., 2020). As there is high positive correlation with the severity of COVID-19 in chronically diseased individuals (Dongarwar et al., 2020; Xia et al., 2020; Gavrilova NS and Gavrilov LA, 2020), it is possible that the host epigenetic factors are the key in dictating the outcome of COVID-19 disease. This review will provide comprehensive information on aberrant epigenetic players and their role in developing chronic diseases and their potential connection with the development of COVID-19 severity.

Angiotensin-converting enzyme 2 (ACE2) receptor and SARS-CoV-2

The ACE2 receptor present on the epithelial cells of the respiratory tract facilitates the entry of life-threatening SARS-CoV-2 into the human system (M Zhong et al., 2020; Sungnak et al., 2020; Stadio et al., 2020). A successful interaction of SARS-CoV-2 with ACE2 receptor is critical for viral entry into the cell, and the reports have confirmed that the receptor-binding domain (RBD) of spike 1 (S1) domain aid the virus

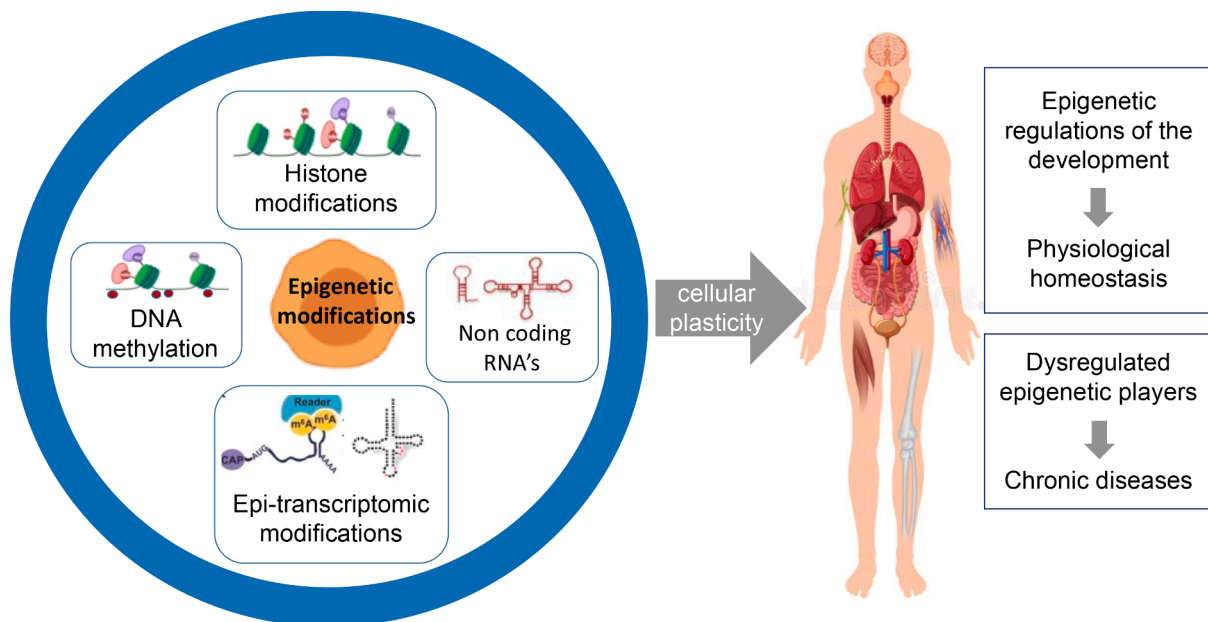


Fig. 1. Depiction of various epigenetic players and its role in gene expression and physiological homeostasis. The major epigenetic players are DNA methylation, histone modifications, epi-transcriptomic modifications on the mRNA and lncRNAs are involved in regulation of precise gene expression during cellular development. The deregulated epigenetic signatures are often associated with the development of various chronic diseases including cancer, cardiovascular diseases, hypertension and chronic pulmonary obstructive syndrome.

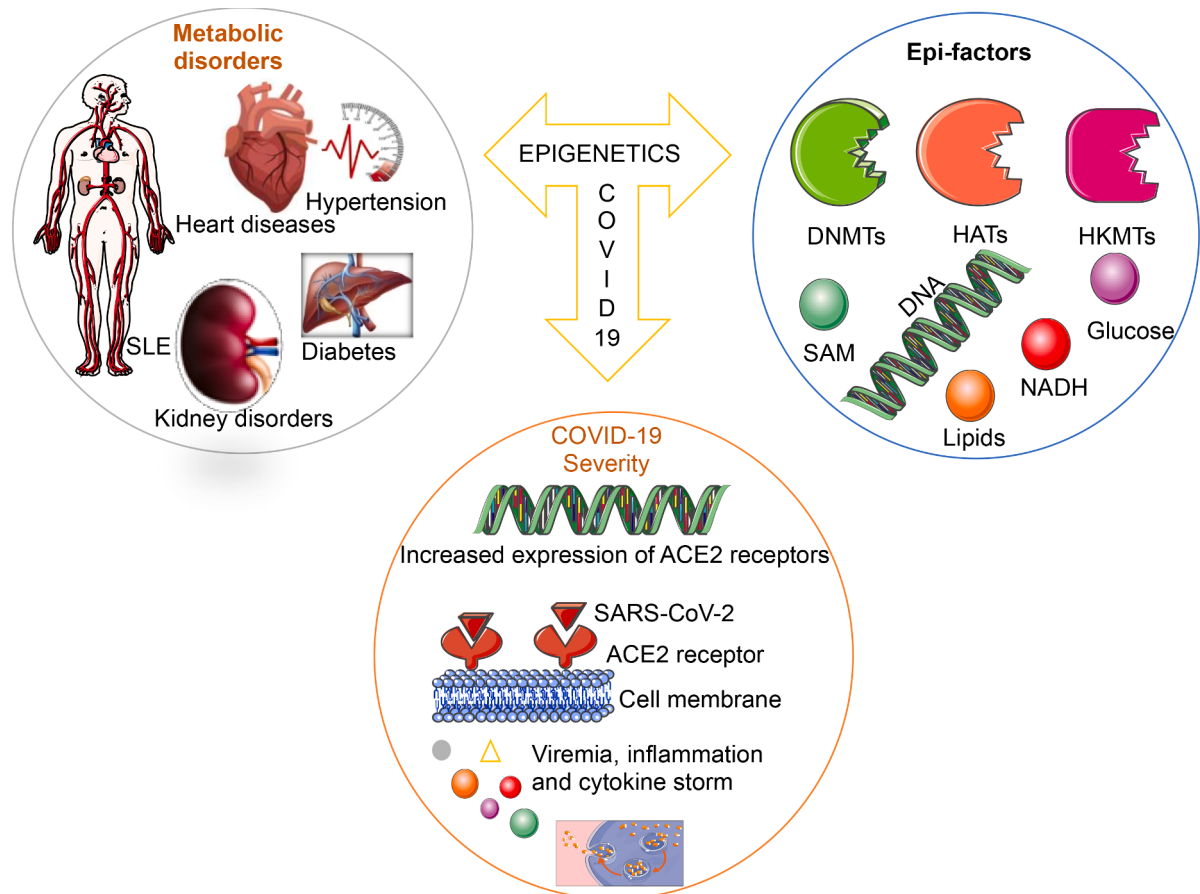


Fig. 2. Schematic representation of various chronic diseases and epigenetic players. A proposed link between aberrant epigenetic signatures in chronic diseases and SARS-CoV2 infection and development of severe form of COVID-19 in chronic diseases individuals.

attachment and spike 2 (S2) domain of the S protein assist the SARS-CoV-2 to penetrate the epithelial cells through the ACE2 receptor (Shang et al., 2020; Lan et al., 2020; Vidwans RR and Lankadasari MB, 2020). Although the binding mechanisms of SARS-CoV-1 and SARS-CoV-2 viruses are similar and use a common ACE2 receptor for their entry into the epithelial cells (Wan et al., 2020), the severity of the diseases and mortality rate are heterogeneous among the SARS-CoV-2 infected individuals (Li et al., 2020). It is proposed that high infectivity of SARS-CoV-2 than other SARS virus is due to the presence of furin like protease cleavage sites in the receptor binding domain. The furin cleavage site is essential to cleave the S1 and S2 fragment of receptor binding domain by furin to mediate the efficient binding and internalization of virus (Peacock et al., 2021; Whittaker GR, 2021). The SARS-CoV-2 has the polybasic insertion (PRRAR) sites at the junction of S1/S2 that can be cleaved by furin protease (Peacock et al., 2021; Whittaker GR, 2021). Whereas, the MERS-CoV uses dipeptidyl peptidase 4 (DPP4) as cellular receptor for its entry into the cells (Wang et al., 2013). In addition to this, altered expression of the ACE2 receptor in the respiratory epithelial cells concerning age, gender, lifestyles and co-morbid individuals may contribute to the COVID-19 severity. It is possible that the aberrant epigenetic landscape at the gene promoter of ACE2 could contribute to the altered expression, and further assist in the development of COVID-19.

Epigenetic control of ACE2 receptor expression

It is reported that the ACE2 receptors are highly expressed in patients with lung damage, heart problems, kidney disorders, and diabetes, which regulate the renin-angiotensin-aldosterone system (RAAS) for a healthy outcome (Arendse et al., 2019; Li et al., 2017; Gheblawi et al.,

2020). Recent reports confirm that the DNA methylation on the ACE2 gene promoter significantly governs its expression (Chlamydas et al., 2020). The presence of hypo or hypermethylation of the CpG islands located in the promoter region of the ACE2 gene and the proportion of the DNA methylation varies in the tissues among the different individuals (Corley et al., 2020; Beacon et al., 2020; Choudhary et al., 2020). Furthermore, the chromatin modifications such as histone lysine methylation, histone lysine acetylation also regulate the activation of the ACE2 receptor expression in humans (Chlamydas et al., 2020). It is also reported that the NAD-dependent histone deacetylases Sirtuin 1 (SIRT1) regulates the ACE2 expression during stress conditions (Clarke et al., 2014; McLachlan et al., 2020). Hence, it is evident that epigenetic players are the key regulators in fine-tuning the expression of the ACE2 receptor in human tissues.

The promoter deletion analysis for ACE2 gene have found that two regulatory regions in the promoter are essential for successful gene expression and it harbor sites for several transcription factors (Pedersen et al., 2013; Beacon et al., 2021; Tie et al., 2018). It is possible that the DNA methylation play key role in regulating the expression of ACE2 gene in the various epithelial cells. The DNA methylome analysis have revealed that significant levels of hypomethylation on the several sites of ACE2 gene promoter in the lung epithelial cells, which explains the increased expression of ACE2 in this tissues (MJ Corley and Ndhlovu, 2020). There were also a report that the variation of the DNA methylation levels on the vicinity of the TSS and ACE2 gene body with respect to age and found significant levels of DNA hypomethylation in females than males (Cardenas et al., 2021). A recent report on global DNA methylation analysis of blood samples from COVID19 and healthy control individuals have clearly shown that significant levels of DNA hypomethylation than hypermethylation (Balnis et al., 2021). Further,

histone epigenetic modifications also play a key roles in the regulation of the ACE2 gene expression. It is reported that increased expression of ACE2 in COVID-19 patients might be due to the histone modifiers viz KAT1, KDAC2 and histone demethylase (Pinto et al., 2020).

The ACE2 receptor is the primary binding protein in the airway epithelial cells for SARS-CoV-2; however it is reported that the TMPRSS2, a well-known membrane-bound serine protease is essential to prime the cleaved spike 2 (S2) subunit protein of SARS-CoV-2 for the successful entry of the virus into the cells (Sanders et al., 2019; Ragia G and Manolopoulos, 2020). In general, it is unknown whether TMPRSS2 expression is regulated through epigenetic modifications, however the DNA methyltransferase 1 (DNMT1) mediated DNA hypermethylation of TMPRSS2 gene was reported in the prostate cancer tissues (Stelloo et al., 2018). Since there are ample evidences of the aberrant epigenetic signature and ACE2 receptor expression in COVID-19 infected individuals, it is worth to investigating on the aberrant expression of TMPRSS2 expression in epithelial cells and its methylome signature for better understanding of the viral entry into cells.

Correlation of aberrant epigenetic signatures and ACE2 expression in chronic diseases

Age, gender, and smoking

The transcriptome analysis of lung samples from patients with severe COVID-19 cases found that the ACE2 was highly expressed than the control individuals (Pinto et al., 2020). Aged individuals and patients with other chronic diseases are found to be at increased risk for SARS-CoV-2 and display a strong association with mortality (Ruan et al., 2020). The male gender shows a trend in DNA hypomethylation of ACE2 gene in the lungs. It is also reported that the testosterone hormone triggers the increased expression of ACE2 and furin protease (Glinsky, 2020). The furin protease assist to cleave the S1/S2 domains of receptor binding domain protein from SARS-CoV-2 for efficient internalization of the virus to the epithelial cells (Peacock et al., 2021; Whittaker GR, 2021). In addition, an increased ACE2 expression was observed in smokers than in the non-smoking counterparts (Leung et al., 2020). This suggests that multiple factors are involved in regulating the expression of the ACE2 receptor in a heterogeneous population, which is in turn regulated by epigenetic players.

Lung dysfunction

Compared to other regions of the human body, airway epithelial cells in the respiratory tract is packed with plenty of ACE2 receptors (Wark et al., 2021; G. Chen et al., 2020). The DNA methylation pattern of the ACE2 gene differs among the normal and lung damaged persons as there was increased expression of ACE2 in damaged lung tissues than normal lungs tissues (Jia et al., 2005; M Zhong et al., 2020; Pruimboom et al., 2020; Xu et al., 2020). Studies in SARS-CoV-2 infected lung disorder patients have revealed that SIRT1 (histone deacetylases) stimulates the high transcription rate of the ACE2 gene by interacting with the promoter region (Pinto et al., 2020; McLachlan et al., 2020). Moreover, it was reported that transcription of the ACE2 associated genes is highly coordinated by the histone modifications viz H3K27ac, H3K4me1, and H3K4me3 (Pinto et al., 2020). The histone acetyltransferase (KAT) and histone lysine deacetylases (KDAC) attenuate the chromatin structure for ACE2 overexpression in lung disorder patients (Pinto et al., 2020). Furthermore, the DNA hypomethylation was observed on the ACE2 gene locus with lung diseases (Pinto et al., 2020; Pruimboom et al., 2020). Hence, the epigenetic machinery of respiratory epithelial cells plays a significant role in governing the ACE2 receptor expression in normal and lung disorder patients.

Diabetes

Elevated expression of the ACE2 receptors was observed in diabetes patients than normal individuals (L. Fang et al., 2020). Moreover, the drugs like ACE inhibitors and angiotensin receptor blockers against diabetes result in the increased expression of ACE2 receptors (Cuschieri et al., 2020). The high glycaemic condition, insulin resistance, with elevated levels of ACE2 receptors favor the vulnerability among diabetic patients to SARS-CoV-2. Patients with kidney diseases like acute kidney injury (AKI) and liver diseases are in the danger zone of SARS-CoV-2 infection and its adverse consequences (Joseph et al., 2020; Fanelli et al., 2020). The ACE2 is playing a significant role Renal-RAS system, and it is highly expressed in the glomerular and tubular regions of the kidney (Soler et al., 2013; Lely et al., 2004). Also, diabetic nephropathy patients exhibited increased expression of ACE2 in these regions (Mizui et al., 2008; Oyelade et al., 2020). The type II diabetes mellitus (T2DM) patients are found to be at high risk for COVID-19. According to reports from CDC, patients with T2DM and metabolic syndrome might have up to ten time's greater risk of death due to COVID (CDC coronavirus reports https://www.cdc.gov/mmwr/Novel_Coronavirus_Reports.html). This could be due to the metabolic state that results in cytokine storm during coronavirus infection, further resulting in multi-organ failure (Mehta et al., 2020). Anti-diabetic medications like GLP1 agonists that improves the metabolic function by inducing the protective activity against competitive binding to ACE2 (Belancic et al., 2021). Due to their anti-inflammatory properties, they are thought to have a positive impact on COVID-19 outcomes (Bornstein et al., 2020). Also, the synthetic protease inhibitor camustat that blocks TMPRSS2 can prevent viral entry and hyperglycemia (Bornstein et al., 2020). Taken together, the elevated expression of the ACE2 receptor in chronic disease patients may facilitate the successful virus entry and further aggravates the COVID-19 disease.

Systemic lupus erythematosus (SLE)

Recent reports had suggested that patients with systemic lupus erythematosus might be prone to severe COVID-19 compared to the normal healthy controls regardless of their immunosuppressive medications (Sawalha et al., 2020; Gartshteyn et al., 2020; Espinosa et al., 2021). The aberrant DNA methylation in SLE patients with the oxidative stress induced by viremia results in the hypomethylation and over-expression of ACE2 (Sawalha et al., 2020). In addition to this, deregulated immune system, hypomethylation at the genes for anti-inflammatory cytokines, and hypomethylated NFκB gene exacerbate the immune response and disease severity by inducing a cytokine storm (Sawalha et al., 2020). It was also found that DNA hypomethylation occurs at the ACE2 gene in the SLE patients and leads to increased expression of ACE2 protein in T cells upon COVID-19 infection (Sawalha et al., 2020). This suggests that, it is very likely that these patients are prone to viral infections, thereby enhancing the dissemination of the SARS-CoV-2 virus.

Kidney disorder

The primary glomerular diseases and nephrosclerosis are the implications of CKD (Chronic kidney diseases). The Renin-Angiotensin-Aldosterone system is an endocrine system in which renin generates angiotensin I (AngI) from angiotensinogen. Ang I turn into AngII through the Angiotensin-converting enzyme (ACE). The AngII has other functions in the kidney through enhancing capillary filtration pressure by arterial vasoconstriction, and contributing to hypertension, further kidney damage (Brand et al., 2013; Lavoze et al., 2012; Ruperez et al., 2003). Expression of the ACE2 gene in renal tissues explains the severities associated with SARS-CoV-2 in CKD patients. Changes in the epigenetic mechanisms are found to be one of the major culprits of chronic kidney diseases (Kato M and Natarajan R, 2019; Park et al.,

2019; Lu et al., 2021). High levels of oxidative stress, advanced glycation end products, pro-inflammatory cytokines, and uremic toxins induce changes in the methylome and acetylation patterns on histones. Chronic kidney disease includes a set of disorders like diabetes, hypertension, CVD, obesity, and others that result in severe kidney damage (Ruster C et al., 2006).

Epigenetics of hypertension, cardio vascular disease and COVID-19

The link between hypertension and COVID-19 is not clear so far. The initial reports have indicated higher hypertension rates among severely ill, hospitalized COVID-19 patients (Zhou et al., 2020; G. Chen et al., 2020; Onder et al., 2020; Grasselli et al., 2020). The severity of COVID-19 illness is commonly observed in the elderly population having hypertension. In contrast, there is no clear evidence of whether this relationship is natural or confounded by age and other co-morbidities associated with hypertension, including obesity, diabetes mellitus, and chronic kidney disease (L. Fang et al., 2020; Richardson et al., 2020). High blood pressure and systemic hypertension are the leading cause of heart failure, stroke and is considered as a common chronic disease (López-Jaramillo P., 2013). The causative factor for the development of hypertension remains unclear; however, several environmental factors contribute to the development of hypertension (Gonzalez-Jaramillo et al., 2019). Several reports have shown that epigenetic changes in the body could profoundly contribute to the development of hypertension (Irvin et al., 2021; Job et al., 2021; Kocken et al., 2020; Ku et al., 2019). A strong correlation was observed in the blood pressure variation and development of hypertension with concurrent changes in the epigenetic landscape, particularly DNA methylation changes (Richard et al., 2017; Kato et al., 2015). Further, aberrant chromatin modification changes and lncRNA activity in response to hypertension are observed in animal model experiments (Liang M, 2018). The correlation of aberrant epigenetic changes and hypertension is evident. Thus, the development of blood pressure and its consequences are due to the multifactorial contribution, of which epigenetic factors could be one of the potential players that may contribute to hypertension. Thus, it is essential to understand epigenetic signaling and hypertension in tackling COVID-19 cases.

The ACE2 receptor is crucial in regulating the function of heart physiology, by acting as a vital controller of the Renin – Angiotensin system (RAS). In addition, the ACE2 acts as a cardio protector by degrading the AngII into Ang 1–7, a vasodilator and regulating the blood pressure (Patel et al., 2016). A recent study has revealed an increased expression of the ACE2 receptors in the tissues of heart disease patients than normal individuals (G. Chen et al., 2020). Moreover, the DNA hypomethylation on the promoter of the ACE2 gene at the CpG4 and CpG5 was observed in the blood samples from hypertension patients (Fan et al., 2017). Also, it is known that during hypertension drug therapy, the cardiac tissues strive to generate more ACE2 protein to balance and recover the body from high blood pressure (South et al., 2020; L. Fang et al., 2020). Overall, there is a trend with the increased expression of the ACE2 receptor in the cardiac patients, which may promote the SARS-CoV-2 entry and increase the risk in the cardiovascular patients.

Host epigenetic players in generation of SARS-CoV-2 virus

The SARS-CoV-2 is highly contagious than SARS-CoV-1 and MERS-CoV viruses, suggesting the rapid viral replication in the host epithelial cells (H Chu et al., 2020). It is proposed that the SARS-CoV-2 may reprogram the host epigenetic modifiers for its replication. The N6-adenosine modifications (m6A) on the RNA emerged as new epi-transcriptomic modifications and the most abundant eukaryotic RNA modification, and it represents over 80% of all RNA methylation (Kim et al., 2020). The m6A modifications on RNA affect the structure,

splicing, localization, translation, stability, and RNA turnover in the cells (Zaccara et al., 2019). It is known that the m6A exhibits both pro-and anti-viral activities, depending on the virus species and host cell type (Dang et al., 2019). The genome sequencing of SARS-CoV-2 has revealed that it contains more than 50 potential m6A sites, recognized by N6-adenine RNA methyltransferases (Wu et al., 2020; Zhang and Holmes, 2020; Wang et al., 2020; Yadav et al., 2020). A detailed investigation is essential to understand whether SARS-CoV-2 RNA is subjected to m6A modifications and its role in virus replication and viral particle synthesis in the host cells. Moreover, a recent report has shown that SARS-CoV-2 protein interacts with host m6A machinery for efficient infection (Zhang et al., 2020).

Reports have shown that the presence of SARS-CoV-2 RNA in serum or plasma of the infected patients, notably 15% of the 41 patients who were first tested positive were detected with viremia. Still the concentration was found to be very low (MJ Huang et al., 2020). A recent study has shown high levels of viremia in critically ill patients than normal patients of SARS-CoV-2 infected cases and hence highly prone to develop severe diseases up to 8 fold (Bermejo-Martin, et al. 2020; Fajnzylber et al., 2020). Another study has reported that COVID-19 cases exhibiting septic shock with enlarged lung and decreased blood oxygen are well correlated with high levels of SARS-CoV-2 viremia and inflammatory markers (G. Chen et al., 2020). Thus, the generation of high titre SARS-CoV-2 viral load is crucial to establish severe illness (Zou et al., 2020). Although ~80% of the infected individuals show only mild symptoms, the host factor that regulates the high viral load and viremia are remains unknown. One of the key factors that might assist in high titre viremia is the overexpression of ACE2 receptors in the alveolar epithelial cells and epigenetic dysregulation in other organs (Sawalha et al., 2020). The COVID-19 disease severity is highly heterogeneous among the infected cases and the host epigenetic players are the key in regulating the viral load and disseminating the virus.

Epigenetic regulation of cytokine storm in SARS-CoV-2

The normal antiviral immune response needs the activation of the inflammatory response pathways of the immune system. An abnormal or magnified response of the host's immune system can lead to severe disease if it stays uncontrolled (Braciale and Hahn, 2013). One of the significant suspected reasons behind the deaths related to COVID-19 is cytokine storm, which is also known as cytokine storm syndrome (CSS), which is an aggressive inflammatory response characterized by the release of a massive amount of pro-inflammatory cytokines (Tisoncik et al., 2012). In addition, the CSS mediated uncontrolled inflammation leads to lung injury, multi-organ failure, and unfavorable prognosis of severe COVID-19, eventually leading to death (Merad and Martin, 2020) (Ruan et al., 2020) (Chu et al., 2005) (MJ Chen et al., 2020) (M Gao et al., 2020).

Mainly two types of cells, such as dendritic cells and macrophages, act as primary defensive walls by sensing the danger signs through direct contacts or by secreting interferons (IFN) and tumor necrosis factor (TNF). So, their epigenome needs to be regulated quickly in response to the external stimulus to prime a quick antiviral response and generate an efficient memory (Schäfer and Baric, 2017). Reports have suggested that the epigenetic regulation of cytokine production is hampered in individuals with SLE (Systemic Lupus Erythematosus). The promoters of the genes involved in inflammation, including the cytokine master regulator NFκB, CD40LG, CD11A, are significantly demethylated in SLE patients, thereby resulting in an increased expression of interferons leading to cytokine storm (Coit et al., 2016). Moreover, previous studies suggested that the expression of IL-6, another important player in the so-called "cytokine storm" occurring in the most severe COVID-19 patients, is modulated by the DNA methylation of promoter of its gene. It is also found that the oxidative stress induced by viral infections, especially SARS-CoV-2 infection, can inhibit the maintenance of DNA methyltransferase DNMT1, thereby aggravating the DNA methylation

defects (Li et al., 2014) (Perl, 2013) (Sawalha et al., 2020). Therefore, in SLE, interferon-regulated genes and inflammatory cytokine genes are hypomethylated and epigenetically primed for transcription upon viral infection mediated interferon release by the immune system, resulting in a cytokine storm.

Unlike the primary immune response genes like IFN (Interferon) and TNF (Tumour Necrosis Factor), which shows poised promoters containing both H3K4me3 and H3K27me3 marks, the interferon-stimulated genes (ISGs) exhibit reduced levels of activation marks (Agalioti et al., 2000) (L. Fang et al., 2012). Another vital signature associated with IFN expression is H3K9me2 modification. It contributes to local DNA methylation and helps in chromatin condensation and hence prohibiting histone acetylation by recruiting the transcriptional repressor of the heterochromatin protein 1 (HP1) family (L. Fang et al., 2012). However, experiments showed the presence of activation marks in the promoters of genes responsible for pro-inflammatory cytokines. The increased level of H3K4me3 in monocytes was observed mainly in areas associated with the promoters of genes responsible for pro-inflammatory cytokines expression, like TNF α or interleukin (IL)–6 and IL-18 when treated with β -glucan (Quintin et al., 2012) (Netea and Van Crevel, 2014). It is also shown that there was an increased levels of H3K4me3 and acetylation at histone 4 of (H4Ac) upon significant stimuli with an immunogen like lipopolysaccharide (LPS) in dendritic cells and macrophages, suggesting a well-organized and specific induction of the innate immune response by epigenetic regulatory mechanisms (S. Mehta and Jeffrey, 2015) (Garber et al., 2012) (Nicodeme et al., 2010). A recent study of the genome-wide DNA methylation analysis has shown that marked epigenetic signatures in the peripheral blood of COVID-19 infected individuals than normal individuals (Corely et al., 2020). They have identified a distinct DNA methylation signature characterized by hypermethylation of IFN-related genes and hypomethylation of inflammatory genes (Corely et al., 2020). Thus, it is evident that IFN and innate and trained immune responses are precisely regulated by specific epigenetic players and may have a significant function during COVID-19 disease (Mantovani A and Netea MG, 2020). Although the SARS-CoV-2 research is in its infancy, these observations offer space for the possibility that epigenetic mechanisms that can play an essential role in developing cytokine storm in COVID-19 patients.

Nutritional epigenetics and COVID-19 disease outcome

The increased mortality rate among SARS-CoV-2 infected individuals with low immunity and pre-existing chronic diseases was observed (Calder PC, 2020; Arunachalam et al., 2020). Therefore, supplementing healthy food and appropriate vitamin doses can lead to more effective and individual-centric therapy in co-morbid cases. Diet or nutrition is one of the decisive factors that induce the long-term changes in DNA methylation pattern on the genome, which influences the health and age-related diseases (Lillicrop et al., 2014; Kim et al., 2009). The nutrients and their by-products can mis-regulate many epigenetic enzymes like DNA methyltransferases and histone acetyltransferases in the cells to induce changes in the expression of critical genes, which further impacting the overall health and longevity (Choi et al., 2010; Davis et al., 2007). Many reports have addressed the influence of diet-induced epigenetic changes in the development of organisms and susceptibility to diseases. For instance, folate, a well-known water-soluble vitamin B, and its metabolism are strongly linked to epigenetic changes (Choi et al., 2010; Kim et al., 2009; Davis et al., 2007). It is also reported that vitamin deficiency leads to an impaired immune response, which promotes increased mortality in chronically diseased individuals. The vitamins are well recognized as an inducer of various epigenetic modifications including methylation, citrullination, acetylation, and phosphorylation, and many of these modifications are associated with gene expression and repression. The transcriptional mediator NF- κ B is highly expressed in acute respiratory distress syndrome (ARDS) and these processes are linked with DNA hypomethylation and vitamin metabolism in the cells

(Colombi et al., 2020). A report also suggests that COVID-19 patients develop severe immune activation in the lungs which further developing into pneumonia (H Chu et al., 2020). The disparity in the nutritional supplement and obesity factor dramatically contributes to the COVID-19 severity (Belanger et al., 2020), these factors may directly or indirectly influence the host epigenetic players and could deregulate the gene expression. Thus, a healthy and appropriate nutritional supplement is highly essential to overcome the COVID-19 related complications in individuals with chronic diseases.

Conclusion

The SARS-CoV-2 is highly contagious than SARS-CoV-1 and MERS-CoV viruses. The mortality in SARS-CoV-2 infected individuals is lower than MERS-CoV virus; however the higher mortality was reported in SARS-CoV-2 infected co-morbid individuals. The COVID-19 associated mortality is strongly correlated with many chronic diseases (Liu et al., 2020), but there is no clear evidence on the host or viral-mediated factors that increase the death rate in COVID-19 patients. The host epigenetic players are the key factors in regulating the cell and tissue-specific gene expression and are strongly influenced by various environmental factors. Aberrant epigenetic signatures are commonly observed in many chronic diseases, including lung disorder, diabetes, hypertension, SLE, kidney disorder, and cardiac hypertrophy. Emerging reports also have indicated that epigenetic regulation of ACE2 receptor expression in the epithelial cells of the respiratory tract is varied among different age groups. Therefore, targeting the host factors along with anti-viral therapy could potentially reduce the co-morbidity among the SARS-CoV-2 infected chronic diseases patients. Further, detailed investigations are required to understand whether deregulated epigenetic signatures in various chronic diseases of the individuals have any role in aggravating the severity of COVID-19. Eventually, the treatment strategies for COVID-19 should be devised based on the patient's chronic diseases status for a successful recovery.

Credit author statement

AR conceived to draft the review and collected supporting literatures. VSD, CAJ and GG collected the literatures and drafted the review on parts. CAJ and GG prepared the figures. SA collected the literature and drafted selected topic. AR collated all the parts and edited the review. All the authors read and approved the final review draft.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest with the contents of this article.

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