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Review Article



## Host's DNA methylation alterations accompanying COVID-19 infection: a review article

Layla Fouad Ali<sup>1</sup>, Fadhel Mohammed Lafta<sup>1</sup>, Basim Mohammed Khashman<sup>2</sup><sup>✉</sup>

<sup>1</sup>Department of Biology, College of Science, University of Baghdad, Iraq.

<sup>2</sup>National Cancer Research Center, University of Baghdad, Iraq.

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✉ Corresponding Author: [basimkh@gmail.com](mailto:basimkh@gmail.com)

### Abstract

The latest global pandemic of severe acute respiratory syndrome (SARS-CoV-2) is triggered by a highly pathogenic RNA virus initiating coronavirus disease 2019 (COVID-19). Epigenetic modifications (mainly DNA methylation and histone modification) are key regulators of the transcriptome. Such epigenetic marks have the ability to switch on/off gene expression. Additionally, the epigenetic marks are known to be dynamic, reversible, and more vulnerable, than the genome, in response to environmental insults including pathogenic invaders such as viruses and bacteria. During the period of COVID-19 pandemic, much more efforts have been concentrated on characterizing the SARS-CoV-2 virus, determining how it enters the cells, and revealing the associated health complications. Interestingly, the SARS-CoV-2 RNA virus is believed to have the potential of hijacking the host immune cells' epigenome to avoid antiviral defense. However, a very little scientific understanding of how the host epigenome responds to COVID-19 infection. This review summarizes the existing knowledge and provides an overview of a considerable amount of literature published on this topic, especially the contribution of DNA methylation alterations in triggering the cytokine storm in pulmonary tissues mainly by the hyper-activation of the immune system and uncontrolled influx of cytokines in response to COVID-19 infection.

**Keywords:** COVID-19 Infection, DNA Methylation, Cytokines Storm.

### Introduction

The latest coronavirus disease 2019 (COVID-19) pandemic has imposed a very serious global health threat and profoundly changed the life around us (Zhao, 2020). COVID-19 arises from the SARS-CoV-2 virus. COVID-19 results in mild to severe respiratory sickness, and can cause death as a consequence of the disease complications. Severe health complications have been linked to COVID-19 infection including organ damage affecting the heart, kidneys, skin, and brain. The cytokine storm refers to the very aggressive immune system that responds to infection, acts directly in defining the severity of a COVID-19 illness, and drives the progress of acute respiratory distress syndrome (ARDS). ARDS is a life-threatening lung injury that permits fluid to leak into the lungs. Consequently, breathing turns out to be difficult leading to a severe shortage supply of

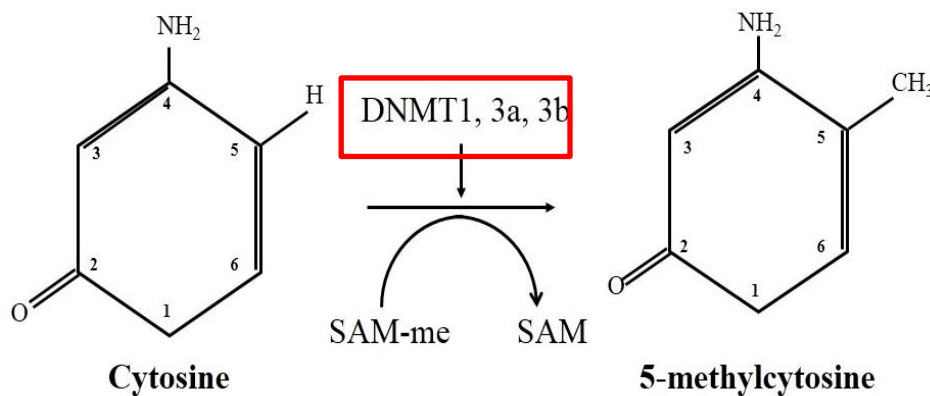
oxygen body (Desai et al., 2022). Epigenetic modifications have a key role as molecular regulators for the transcription activity of the genome. These modifications, involving DNA methylation, histone modifications, and siRNA, are considered the guardian of the genome, responsible for maintaining genomic stability and regulating gene expression that influences the resultant cellular phenotype. DNA methylation occurs when enzymes called DNA methyltransferase (DNMTs) bind adenine and cytosine bases to methyl groups, which represses gene expression (van et al., 2013). Early in the pandemic, it is believed that the SARS-CoV-2 virus was capable of changing its host's epigenetic profile through the disruption of DNA methylation marks (Behura et al., 2022). While the exact mechanism by which the virus triggers this methylation is unclear, studies have provided novel insight into the impact these epigenetic changes have on the host immune response upon COVID-19 infection. However, an association between COVID-19 infection and reduce expression of epigenetic machinery

(including DNMTs) was suggested by the finding of a recent study (Salem et al., 2023). The following sections will discuss in detail the impact of COVID-19 infection on epigenetic modifications and the regulation of cytokine storms during such infection.

### DNA methylation pattern across the genome of healthy cells

DNA methylation is an epigenetic modification that consists of the binding of a methyl group to a cytosine nucleotide. The genome methylation is catalyzed by three epigenetic modifiers called DNA methyltransferases (DNMT1, DNMT3a and DNMT3b). These enzymes utilize S-adenosyl-methionine as a methyl donor to convert unmethylated cytosine into methylated

one (Fig. 1). Across the genome, the vast bulk of DNA methylation arises in the position of a CpG dinucleotide (i.e. a cytosine directly followed by guanine that is known as a CpG site) (Ryan et al., 2009; Noroozi et al., 2021). Generally, CpG sites cover almost 1% of the human genome; however, they are underrepresented in the genome. This is possibly due to the relatively high spontaneous deamination of 5'-methylcytosine (5mC) to thymine. Interestingly, CpG sites are not randomly distributed across the genome, where up to 85% of these CpGs are methylated and largely located within the genome's repetitive regions. While the rest of the genome CpGs ( $\approx 15\%$ ) are mainly methylation free and clustered preferentially in short DNA sequences called CpG islands (Baylin and Ohm, 2006).



**Fig. 1** Catalyzing the conversion of cytosine into 5-methylcytosine via the act of DNA methyltransferase enzymes (DNMT1, 3a and 3b).

The main function of DNA methylation in healthy cells can be summarized as follows:

#### Maintain genomic stability and suppression of mobile elements:

DNA methylation marks have a crucial role in conserving genomic stability via suppressing and silencing the activity of mobile elements. Mobile elements (also known as endo-parasitic sequences) are widespread genomic repetitive sequences that are capable (when they are activated) of duplicating and inserting themselves in diverse genomic regions inducing genomic instability and increasing mutation rate (Goodier and Kazazian, 2008). To minimize the transcriptional noise in healthy cells, mobile elements are preferentially silenced and inactivated via DNMT hypermethylation to suppress their mobilization and ensure chromosomal stability (Pappalardo et al., 2021).

#### Genomic imprinting and X-chromosome inactivation:

Another key role for DNA methylation in healthy cells is the regulation of genomic imprinting contributing to the monoallelic expression of the associated gene. In this process, DNA hypermethylation at the promoter region of one of the two parental alleles of a given gene is necessary for genomic

imprinting to ensure single allelic expression. Similarly, DNA methylation is required for the inactivation of one of the female X-chromosomes (Bartolomei et al., 2020). This epigenetic dosage reduction effect ensures that males and females have the same expression level of genes mapped to the X-chromosome. Interestingly, ACE2 maps to chromosome X and can escape the aforementioned epigenetic inactivation. Such reactivation of the epigenetically inactivated gene, ACE2, could potentially explain the higher ACE2 expression observed in females which is accompanied by a higher COVID-19 infection rate than that of males (Cardenas et al., 2021; Foresta et al., 2021).

#### Regulation of tissue-specific gene expression:

Although all of the normal cells in the body possess similar DNA sequences most cells do not produce all possible proteins, a selection, depending on the type of cell. This is largely because cells have dissimilar epigenetics marks that govern gene expression and the resultant proteins. Consequently, tissue-specific gene expression is somewhat controlled by the different DNA methylation marks they have (Loyfer et al., 2023).

#### DNA Methylation and Cytokines Storm

The host immune response to the COVID-19 infection is

typically taking the form of a cytokine storm to face the viral invasion. This cytokine storm process is marked by an extreme rush of immune cells to infection sites (commonly upper and lower respiratory tract mainly windpipes and lungs). Cytokine storm in response to COVID-19 infection assigns a very challenging immunological task for the host body, especially in the elderly, immunocompromised, and chronically ill patients (Dey et al., 2023). Because of the acute immune cell influx, normal cell-to-cell interactions and cellular structures are disrupted resulting in severe inflammation, lung injury, acute respiratory distress syndrome (ARDS), tissue damage, and multi-organ failure that potentially causes death in COVID-19 patients (Ragab et al., 2020). Cytokine storm has been linked to increasing COVID-19-related mortality because of the out-of-control over-production and release of inflammatory markers that can contribute to damage to the delicate lung structure. Such host

immune response storm is normally initiated following the viral detection through pattern recognition receptors (PRRs). This activates key transcription factors for instance interferon regulatory factors (IRFs) and NF $\kappa$ B, that afterwards drive the upregulation of sets of genes which include cytokines and interferons. COVID-19 pathogenicity seems to be influenced by epigenetic modulations. Upregulation of ACE2 protein expression through promoter DNA hypomethylation is connected to increased vulnerability to SARS-CoV-2 infection (Rath et al., 2021; Daniel et al., 2022). Following the infection, pro-inflammatory cytokines and chemokines expression are boosted via the promoter demethylation of NF-k, IFN-related genes, and other essential cytokine genes (Foolchand et al., 2022). Other key host immune response cytokines showed to be activated by promoter DNA hypomethylation including ARID5A, CD226, CD244, IL1R1, and STAT6 (Table 1).

**Table 1. Cytokines with altered DNA methylation status during COVID-19 infection**

Gene	Function and its association with cytokines storm during COVID-19 infection	Methylation status upon COVI-19 infection
ARID5A	Regulates host inflammatory response and is possibly involved in autoimmunity (Calzari et al., 2023).	Hypomethylated
CD226	Induces T-cell proliferation and cytokine secretion (IL2, IL5, IL10, IL13, and IFNG) (Godoy et al., 2022).	Hypomethylated
CD244	Activates immune cells and connected to tissue infiltration and vital organs defection in severe COVID-19 patients (Brown et al., 2023).	Hypomethylated
IL4	Regulates antibody production, and inflammation related to reduced serum cytotoxic effector molecules in severe COVID-19 patients (Saraei et al., 2021).	Hypomethylated
IL1R1	Regulate cytokines boost immune and inflammatory responses. Linked venous thrombosis - COVID-19 complications (Yang et al., 2022).	Hypomethylated
STAT6	Involved in increased IL4 and IL3 levels in the lungs of COVID-19 cases (Kgatle et al., 2021).	Hypomethylated
FCGR	Initiates cellular responses to pathogens and supports opsonized antigens phagocytosis (Barturen et al., 2022).	Hypermethylated
IFI27	Modifies the host innate immune response during viral infection (Balnis et al., 2021).	Hypomethylated
EPSI1	Regulates macrophage differentiation (Bowler et al., 2022).	Hypomethylated
IRF7	Essential for innate immunity (Konigsberg et al., 2021).	Hypomethylated

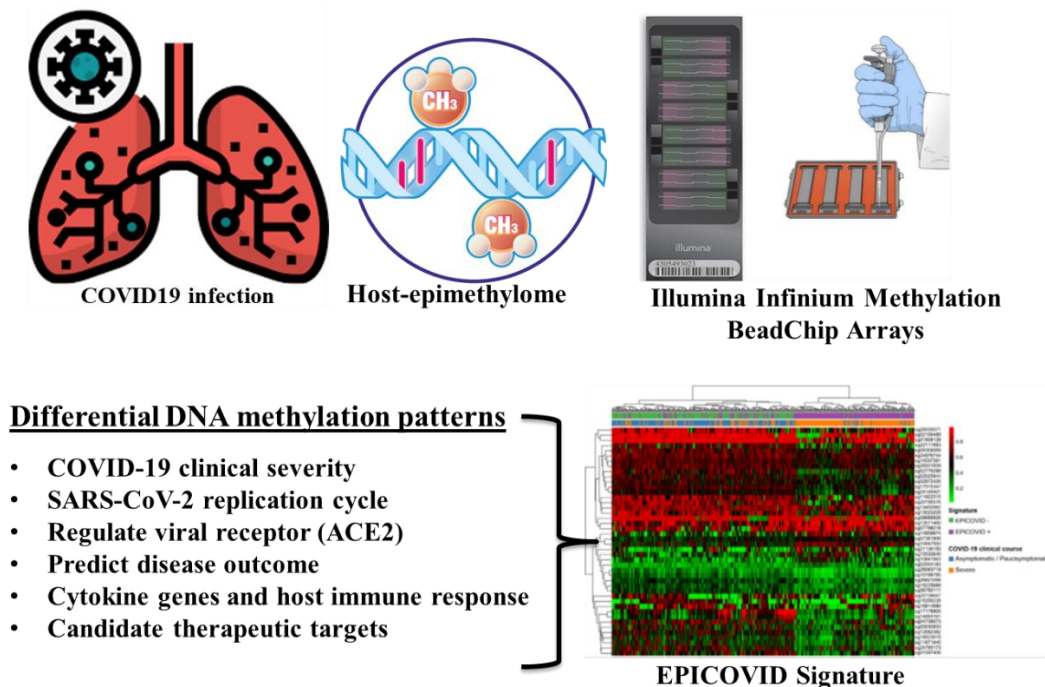
### Genome-wide DNA methylation alterations associated with COVID-19 infection

Epigenetic modulations upon viral infection have been proposed to be both a defense approach and a result of the pathogenic influence. Whereas the majority of COVID-19-conducted studies emphasized the host inflammatory and immune-mediated responses to infection, to date, little is known about epigenetic alterations in response to SARS-CoV-2 infection. Recently, efforts have concentrated to understand how the host epimethylome reacts to the SARS-CoV-2 virus aiming to identify novel epigenetic alterations mediated inflammatory response to COVID-19 infection. A number of studies have explored the host DNA methylation pattern at the global level utilizing high throughput genome-wide (GW) DNA methylation array from Illumina Infinium Methylation BeadChip 450K and 850K array

platforms that cover 450,000 and 850,000 of the genome CpG site (Fig. 2). These studies have come out with interesting findings regarding identifying COVID-19 asymptomatic patients and predicting the different clinical outcomes of the diseases (Arnold et al., 2022). As detecting asymptomatic COVID-19 infections is one of the mysteries of the COVID-19 pandemic, genome wide DNA methylation profiling via assessing the global genome CpGs variations has shown its utility in distinguishing asymptomatic from those symptomatic patients and healthy uninfected individuals as well. Such differentially methylated signatures could provide an explanation as to why some people infected with SARS-CoV-2 get incredibly ill, whereas some people get no symptoms at all. The main findings of almost all of the published genome-wide-DNA methylation studies are summarized in the below table (Table 2).

Table 2. Genome-wide DNA methylation alterations associated with COVID-19 infection

Approach	Cases investigated/ Country	Findings and References
Illumina Infinium Methylation EPIC BeadChip (850 K/ 450K arrays)	SARS-CoV-2-positive-COVID-19 cases with different disease severity vs. uninfected controls- (USA).	Distinct differentially DNAm profile of severe COVID-19 marked by increased methylation of IFN-related pathways and decrease methylation of inflammatory-pathways-related genes (Arnold et al., 2022).
	COVID-19 patients with different disease severity vs. healthy individuals (China).	Differentially DNAm genes were enriched to signal transduction and immune system of the severe vs. mild group; marked by downregulation of <i>GNG7</i> and <i>GNAS</i> expressions in the severe COVID-19 cases (Zhou et al., 2021).
	COVID-19 patients with comorbidities vs. severe vs. mild prognosis (Italy).	Poor prognosis of COVID-19 patients exhibited dysfunction of the epigenetic maintenance system marked by a significant increase in the stochastic epigenetic mutations (Calzari et al., 2023).
	COVID-19 patients hospitalized and not hospitalized with different clinical course (Spain).	DNA methylation signature (EPICoVID of 44 CpG sites) associated with the clinical severity of COVID-19, including <i>AIM2</i> , <i>HLA-C</i> genes (de Moura et al., 2021).
	COVID-19 patients with longitudinal follow up during disease severity and healthy controls (USA).	Significant GW differential methylation signature associated with COVID-19 cases vs. healthy controls. Among DM sites, genes/pathways related to in interferon signaling and viral response (e.g. IRF7, OAS1) were significantly enriched (Konigsberg et al., 2021).
	Pair samples of prior and following confirmed COVID-19 diagnosis (USA).	DM CpGs were identified following confirmed COVID-19 infection, with an obvious impact of vaccination in modulation the epigenetic signature (Pang et al., 2022).
	Case-control study on COVID-19 patients vs. uninfected controls (China).	Significant cell-type specific DNA hypermethylation lowering the expression of gamma-delta T cells immune and virus-related signaling pathways genes ( <i>S100A9</i> , <i>AHNAK</i> , <i>CX3CR1</i> , <i>TRAF3IP3</i> , and <i>LFNG</i> ) in COVID-19 patients (Wang et al., 2022).
	COVID-19 patients with different disease severity vs. healthy controls (USA).	DM patterns discriminate asymptomatic from symptomatic COVID-19 infection. DNA methylation of genes including – but not limited to – <i>FBXO16</i> , <i>PSD3</i> , and <i>RAE1</i> in asymptomatic patients compared to symptomatic patients (Arnold et al., 2022).
	COVID-19-recuperation cases compared to uninfected individuals (Sweden).	Differential DNA methylation profiles differentiate COVID-19 recuperation from uninfected controls. Differential DNA methylation patterns associated with Wnt, mAChRs signaling, and GnRH receptor pathways (Huoman et al., 2021).
	SARS-CoV-2-negative vs. SARS-CoV-2-positive cases (Spain).	Differential DNA methylation patterns distinguish mild from severe COVID-19 patients. Key immune components including cytokines and IL-6 expression were altered via epigenetic modulation of the transcription activity of CEBP (Barturen et al., 2022).
	COVID-19 cases with ARDS under mechanical ventilation vs. non-infected healthy subjects(Qatar)	Differential promoter DNA methylation patterns of genes regulating immune-related pathways including interferon-gamma/ alpha of innate and adaptive antiviral immune responses (Bradic et al., 2022).
	COVID-19 patients vs. healthy controls (China).	Differentially methylated genes differentiate COVID-19 from uninfected individuals. Genes ( <i>CENPM</i> and <i>KNL1</i> ) involve in coronavirus replication and transcription were found to be epigenetically activated (Bohlin et al., 2022)
	Hospitalized COVID-19-positive and COVID-19-negative cases vs. healthy controls samples obtained before the pandemic (USA).	Global DNA methylation levels did not separate COVID-19 patients from pre-pandemic healthy controls. However, differentially methylated CpGs were identified to predict COVID-19 severity and enrich to immune response to viral infection /leukocyte activation (Balnis et al., 2021).
	COVID-19 patients vs. healthy controls (Norway).	CpGs maps to genes related to SARS-CoV-2 host cell entry associated with both age and sex, excepting <i>ACE2</i> receptor gene (maps to X-chromosome), only associated with sex (pFDR<0.01) (Bohlin et al., 2022).
	Case-control study on COVID-19 patients vs. uninfected controls (China).	Distinct DNA methylation patterns of several genes with key roles in regulating immune cell functions ( <i>NHLH2</i> , <i>ZEB2</i> , <i>NWD1</i> , <i>ELOVL2</i> , <i>FGGY</i> , and <i>FHL2</i> ) among the different age group of patients with COVID infection (Chen et al., 2022).
	COVID-19 negatives and positives (with different severity/complications, UAS, Netherlands and others).	Different DNA methylation patterns, especially in <i>ACE1/2</i> , can be (in part) related to the differential susceptibility, symptom severity and death rate for COVID-19 (Steyaert et al., 2020).
	Young adults before, during, and after asymptomatic and mildly symptomatic COVID-19 infection (USA).	Epimethylome profiling was unable to distinguish asymptomatic or mildly symptomatic COVID-19 infections. A number of DM sites persevered for months of follow-up, with a pattern similar to autoimmune/ inflammatory disease (Mao et al., 2023).
COVID-19 patients compare to COVID-19 negative controls( Spain and USA).	Epimethylome signature predicts COVID-19 patients from patients presenting with respiratory symptoms (with 96.87-100% accuracy). A panel of 7 CpG sites was able to distinguish COVID-19 severe and mild cases from healthy individuals (Zhang, 2022).	



**Fig. 2 Genome –wide DNA methylation approach for identifying EPICOVID-host associated signature**

**Future Prospective**

As epigenetic modifications illustrate to have substantial changes with age affecting gene regulations and cell functions during the aging process, it would be interesting to investigate how these epimethylome changes influence underlying mechanisms of aging-associated immunodeficiency against SARS-CoV-2. Studies also have consulted that the altered DNA methylation signature upon COVID-19 infection can impact the expression of genes regulating the disease progression and having the potential to be targeted in the infection clinical management. Analyzing epigenetic changes in COVID-19 patient DNA could be the key to not only identifying the virus in asymptomatic patients but also helping us to get one step closer to understanding what causes the different clinical outcomes in COVID-19. The identified differential DNA methylation sites could be utilized to identify COVID-19 patients with paucisymptomatic clinical status from those who will require hospitalized oxygen therapy, and additional organ support measures. In respect to the interaction between host epimethylome and SARS-CoV-2 infection, future studies should define whether these DNA methylation alterations induce antiviral host-protective defense or promote the virus epigenome-hijacking approach to avoid host defense.

**Conclusions**

Overall, the reviewed studies have highlighted the involvement of COVID-19 infection in modulating the host epigenetic landscape affecting key components of inflammatory response pathways (including the triggering of cytokines storm).

Additionally, DNA methylation profile was able to distinguish asymptomatic from symptomatic COVID19 patients. Furthermore, the altered host DNA methylation marks during COVID-19 infection were able to predict the disease severities and patient outcomes. The reviewed evidence demonstrated how epigenetic testing could be of great use to identify the virus in asymptomatic members of the population. This could prove to be beneficial for the surveillance and containment of the virus, and thus help to prevent any further outbreaks of COVID-19.

**Conflict of Interest**

The author hereby declares no conflict of interest.

**Consent for publication**

The author declares that the work has consent for publication.

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