



Review

Epigenetic regulation of the COVID-19 pathogenesis: its impact on the host immune response and disease progression

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Abstract: Coronavirus disease 2019 (COVID-19) is highly infectious and may induce epigenetic alteration of the host immune system. Understanding the role of epigenetic mechanisms in COVID-19 infection is a clinical need to minimize critical illness and widespread transmission. The susceptibility to infection and progression of COVID-19 varies from person to person; pathophysiology substantially depends on epigenetic changes in the immune system and preexisting health conditions. Recent experimental and epidemiological studies have revealed the method of transmission and clinical presentation related to COVID-19 pathogenesis, however, the underlying pathology of variation in the severity of infection remains questionable. Epigenetic changes may also be responsible factors for multisystem association and deadly systemic complications of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infected patients. Commonly, epigenetic changes are evoked by alteration of the host's immune response, stress, preexisting condition, oxidative stress response, external behavioral or environmental factors, and age. In addition, the viral infection itself might manipulate the host immune responses associated with inflammation by reprogramming epigenetic processes which are the susceptible factor for disease severity and death. As a result, epigenetic events such as histone modification and DNA methylation are implicated in regulating pro-inflammatory cytokines production by remodeling macrophage and T-cell activity towards inflammation, consequently, may also affect tissue repair and injury resolution process. This

review aims to discuss the comprehensive understanding of the epigenetic landscape of COVID-19 disease progression that varies from person to person with supporting interdisciplinary prognosis protocol to overcome systemic impairment.

Keywords: epigenetic modification; COVID-19 pathogenesis; ACE2 receptor; immune response; cytokines storm; respiratory illness; viral replication; genomic expression; systemic impairment; epigenetic therapeutics

1. Introduction

A diverse coronavirus strain infected several species for centuries, but there is a lack of significant brief history of non-human exposure and infection. However, the first human coronavirus infection was reported around mid-1960 when two strains OC43 and 229E were detected as respiratory viruses [1,2]. These respiratory viruses were named corona due to their distinctive spike structure with rounded tips on their circular surface [3]. The molecular components of viral gene replication and the pathophysiology of host cell infection by the coronavirus's family have been an active field of research since the 1970s but most newly emerged human coronaviruses were characterized and specified after 2000 [3,4]. The worldwide outbreak of human coronavirus infection was reported in late 2002, later named severe acute respiratory syndrome (SARS-CoV), therefore a group of researchers also identified a new human coronavirus named MERS-CoV (middle east respiratory syndrome coronavirus) which causes an outbreak of pneumonia in the middle eastern region in 2013 [5,6]. MERS-CoV was a mutated version of SERS-CoV, which appeared to be more fatal and easily transmissible than the previously discovered coronavirus strain [7]. Notably, the SARS-CoV-2 virus is a single-stranded RNA-based enveloped virus encoded by 9860 amino acids in 29881 bp of size length [8,9]. Gene expression of SARS-CoV-2 is mediated by structural and non-structural proteins, these proteins are viable to sustain the circle of the infection stage and are also important targets for potential antiviral therapies [10]. A large number of glycosylated structural proteins cover the outer surface of SARS-CoV-2 called spike or S protein which promotes the viral entry into the host by binding with the host cell angiotensin-converting enzyme 2 (ACE2) receptor [11,12]. After entering the virus into the host cell, release the viral RNA, then start the replication machinery to reproduce or multiply the viral RNA genome via the host cell (transcriptase-replicase) enzyme complex [9,13]. Structural proteins are synthesized in the process of packaging and assembling the viral genome then it is integrated into the structure of microbes, sequentially it is released from the host cell as new infectious agents and attacks multiple host cells [12,14]. Immediate actions of the innate immune system including successful recognition and activation of signaling cascades play a critical role to de-escalate SARS-CoV-2 infection and provide a shield to save lives from a severe life-threatening infection.

A large number of researchers have been working on potential therapy and vaccines targeting various structural genomic proteins. However, there is less documentation on the anticipation or prognosis of individual severity of viral infection. Because most people remain asymptomatic during the incubation period, and it is difficult to predict the severity of symptoms and outcome of illness to assemble the potential therapy [15]. However, it was believed that respiratory viruses have been usually transmitted in three ways; contact transmission, respiratory droplet transmission, and

airborne transmission [16]. Initially, the surface transmission was the main concern as a main route of transmission, but the latest research claimed that the COVID-19 virus cannot survive on inanimate surfaces for a long time [17,18]. Recent studies suggest close contact or airborne droplet transmission is a more likely route of COVID-19 virus infection, So the Center for Disease Control (CDC) has updated its infection control guidelines to advise people to wear facemasks or shields to prevent the airborne spread by encouraging on improving indoor air quality and ventilation as well as avoiding crowded place [17,19]. Therefore, it is challenging to fully understand the transmission route or assess the transmission risk of COVID-19 infection. So more effective research is required to understand the behavior of the new COVID-19 strain to confront the pandemic.

So, there will be another possible way to control the viral infection by modifying the targeted epigenetic changes of the host cell [20]. Host gene expression patterns maintain the tissue environment to regulate the cellular mechanism and immune response against viral pathogenesis. Epigenetic modification interferes with the regulatory machinery of the host epigenome which may lead to creating a favorable environment for viral replication and pathogenesis [21]. DNA methylation and chromatin looping play important roles to activate and differentiating T cells in the expression of various cytokines IL4, IL5, IL37, and interferon during tissue injury by viral infection. However, histone modification plays an important role to regulates macrophage homeostasis by maintaining the secretion and functions of the inflammatory cytokines. Epigenetic modification has increasingly drawn attention in COVID-19 therapeutic strategy because it may have a role in controlling severe cytokine storms and risks of life-threatening infection. So, this review will discuss the pathogenesis associated with epigenetic regulation and interdisciplinary SARS-CoV-2 prognosis protocol to prevent the multisystem association.

2. The role of epigenetic changes on SARS-CoV-2 pathogenesis

2.1. Viral entry

Host cell invasion is regulated by a viral outer surface glycosylated protein called spike protein which has two domains, S1 promotes the binding to the host cell receptor, and S2 fusion peptides facilitate the viral entry to the host cell [22]. Metalloproteinase, ACE2, associated proteases, and co-receptors dipeptidyl peptidase-4 (DPP4) act as a mediator for SARS-CoV-2 host cell entry [23,24]. The outer surface spike protein S1 shows a strong binding affinity to the receptor in human airway epithelial cells named angiotensin-converting enzyme 2 (ACE2) [25]. Following binding with the receptor, proteolytic cleavage and viral invasion are activated by transmembrane protease serine 2 (TMPRSS2) in the respiratory tract epithelium. The highest binding affinity with ACE2 and the presence of proteolytic cleavage sites in spike proteins are the responsible factors for the high rate of SARS-CoV-2 virus transmission and infection [11,25]. Angiotensin-converting enzyme (ACE) and ACE2 have counter functions in the regulation of the renin-angiotensin mechanism to control blood pressure. ACE converts the angiotensinogen to angiotensin II which acts as a vasoconstrictor to increase the pressure in the peripheral blood vessel [26]. However, ACE2 serves as a vasodilator by hydrolyzing the angiotensin II to angiotensin (1–7) and is abundantly expressed on vascular endothelial tissue throughout the body but highly expressed in renal epithelial cells, gastrointestinal enterocytes, cardiomyocytes, heart pericytes, lung alveolar epithelium, testis and liver [4,24]. The expression pattern of the ACE2 receptor is higher in the upper respiratory tract, profusely found in

the epithelial cells of the larynx, bronchi, tonsils, and nasal cells compare to the lower respiratory tract [4]. Disease severity and high transmissibility of SARS-CoV-2 infection are mainly dependent on the host cell's ACE2 expression and binding affinity of receptors to microbes [27]. Experimental studies on lung tissues revealed that ACE2 expression had increased in the older age group and comparatively decreased in infants and young children [4,28]. So, mortality rate is higher in old SARS-CoV-2 patients due to a large amount of ACE2 available to promote the entry of the SARS-CoV-2 virus inside the host cell [29].

Epigenetic changes may influence the gene regulation of ACE2 receptor expression without changing of underlying DNA sequence, the alteration of ACE2 expression in SARS-CoV-2 infections may result from DNA/RNA methylation or histone modification [30]. ACE2 receptor expression is regulated transcriptionally and post-transcriptionally in the host cell, the epigenetic process plays a vital role to influence the gene expression of the ACE2 receptor. These gene expressions are programmed to work depending on the structural organization or chemical composition of chromatin on DNA and binding protein, histones including phosphorylation, methylation, acetylation, and ubiquitylation [31,32]. Existing pathological condition on infection induces the oxidative stress response, and cytokines infiltrations, and further activate DNA methylation which promotes the overexpression of the ACE2 gene [33]. SARS-CoV-2 infections with high viral load lead to increase expression of the interferon-stimulated gene (ISG) in host cells which evokes the micro RNA targeting upstream promoter's transcription of ACE2 receptor [34]. An imbalance of ACE and ACE2 expression leads to increase viral load vasodilation, and increase secretion, and promotes a severe state of lung infection (Figure 1) [35].

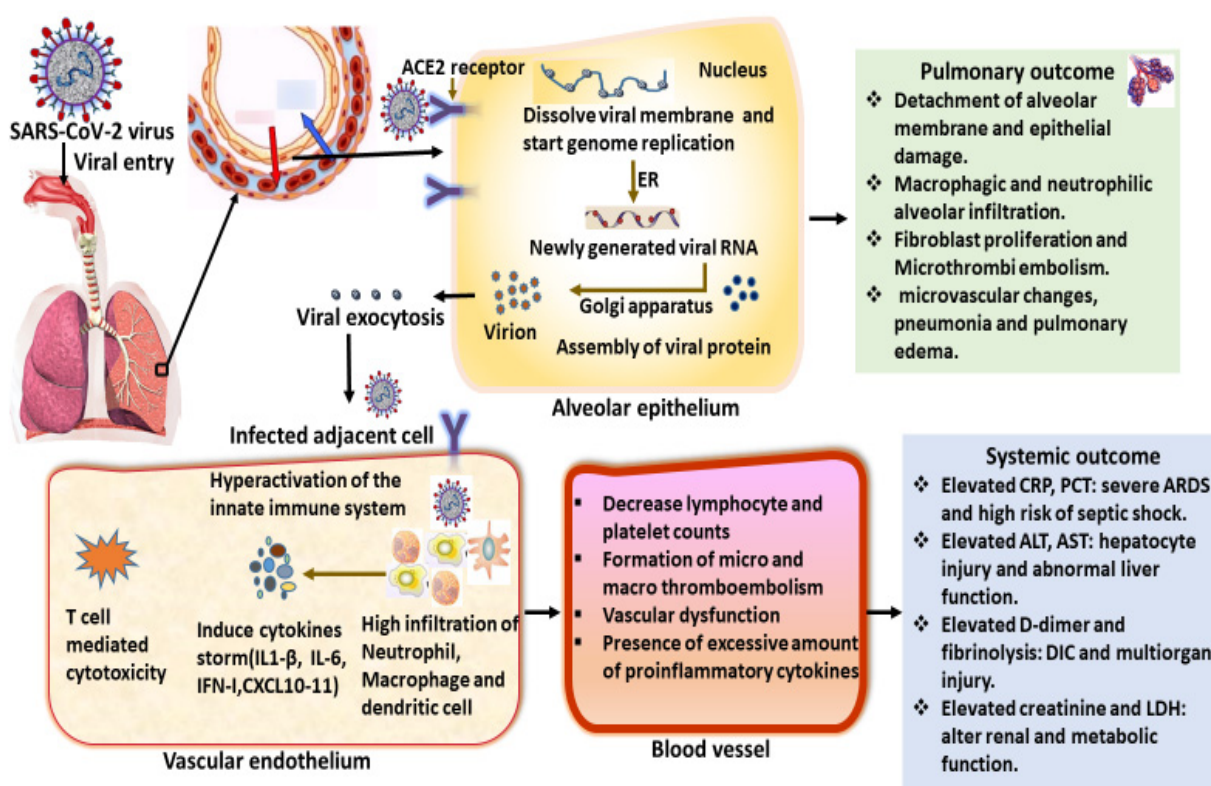


Figure 1. Schematic illustration of SARS-CoV-2 pathogenesis through lungs and systemic circulation with a hypothetical presentation of pulmonary and systemic

involvement of SARS-CoV-2 infection that is associated with critical life-threatening outcomes. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme 2; ER: endoplasmic reticulum; CRP: C reactive protein; PCT: procalcitonin; ALT: alanine transaminase; AST: aspartate transferase; DIC: disseminated intravascular coagulation; LDH: lactate dehydrogenase.

2.2. Host cell interaction

After viral entry, initially, the innate immune system is activated in the airways which are mediated by alveolar macrophages, dendritic cells (DC), and epithelium. Therefore, antigen-presenting DC cells and macrophages attract the virus-specific T cells at sites of infections and initiate the adaptive host cell response against the virus. CD8⁺ and CD4⁺ T cells play a key role to eliminate the virus-infected cells which result in mild symptoms to recovery in most patients [36]. Patients who develop severe respiratory infections with multiple organ involvement are due to SARS-CoV-2 elicited uncompromising inflammatory nature of alveolar damage. Acute respiratory distress syndrome and pathological changes of pulmonary structure are mainly resulting from a sudden increase of pro-inflammatory cytokines (cytokines storm) including granulocyte-colony stimulating factor (G-CSF), IL-6, IL-10, tumor necrosis factor (TNF)- α and interferon (IFN)- γ which accumulate in the alveolar space and eventually causes lung parenchymal injury [16,37,38]. Capillary leakage, thrombus formation, coagulopathy, and Intra alveolar hemorrhage can also be developed in COVID-19 patients inconsistent with the outcome of cytokines storm which causes cardiovascular abnormality and multi-organ dysfunction (Figure 1). Host immune response against SARS-CoV-2 infections varies from person to person and is modulated by epigenetic regulation of immune cells under the effects of extrinsic and intrinsic factors. A number of studies provide evidence of abnormal epigenetic modification can develop as unfavorable outcomes of aging, stress, infectious disease, drug abuse, metabolic disturbances, and so on.

3. DNA methylation regulates the expression of the host immune system

Host epigenetic machinery has been associated with the establishment of immune cell development, differentiation, and activation including blood-derived T cells and tissue-specific macrophages during innate or adaptive immune response [39,40]. The epigenomic mechanism is a highly integrated process that allows or prevents the DNA transcriptional machinery to regulate the gene expression elements such as promoters, enhancers, and silencers in chromatin accessibility for activation or silencing of the targeted gene expression [41]. Epigenetic events such as DNA methylation, repressive histone methylation (trimethylation of lysine 27 residue of histone 3 (H3K27me3) and H3K4me have widely targeted repressing/silencing marker of transcription while activating histone modification and acetylation acts as promoters and enhancers for transcription during maintenance of homeostasis and immune response [41,42]. This important epigenetic modulation in the immune system is guided by epigenetic-regulatory enzymes DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) as well as autonomous and bioenvironmental status [43]. CPG islands of chromatin act as promotor sequence for DNA methylation which also controls the level of gene transcription (Figure 2) [44]. Activated T cells are directly associated with inflammatory response and tissue regeneration in the cascades of growth

factors and cytokines production. DNA methylation may cause the downregulation of TLR4 receptor expression in epithelial cells to sustain the hyperresponsiveness of the immune system epigenetically. This process is the significant portion for recovery to mild symptoms in SARS-CoV-2 infection. However, the epigenetic process acts as an optimal molecular phenomenon for controlling the host immune cell function, which continues activity in a specialized manner, but is also able to adjust or be influenced by surrounding conditions or retrospection of pre-exposure factors. For example, increase free radical production or high salt condition alters H3K4me3 at multiple loci in macrophages, facilitating the NO release upon LPS stimulation which decrease anti-inflammatory phenotypes and increase pro-inflammatory cytokines coincidentally delaying or worsening the injury resolution [45,46]. Indeed, DNA methylation machinery interferes with the T cell homeostasis for anti-inflammatory tissue regeneration so DNMT inhibitor can be used to accelerate the T cell-mediated tissue repairing process in lung injury by increasing the T cell numbers and actions in lung inflammation [46,47]. Aberrant immune response to several microbial infections induces the DNMT dependent DNA methylation which contributes to the reduction of differentiation of CD4+ T cells and subsides the ISC-associated gene proliferation, epigenetic memory may further interfere with the host immune response to SARS-CoV-2 infections [21].

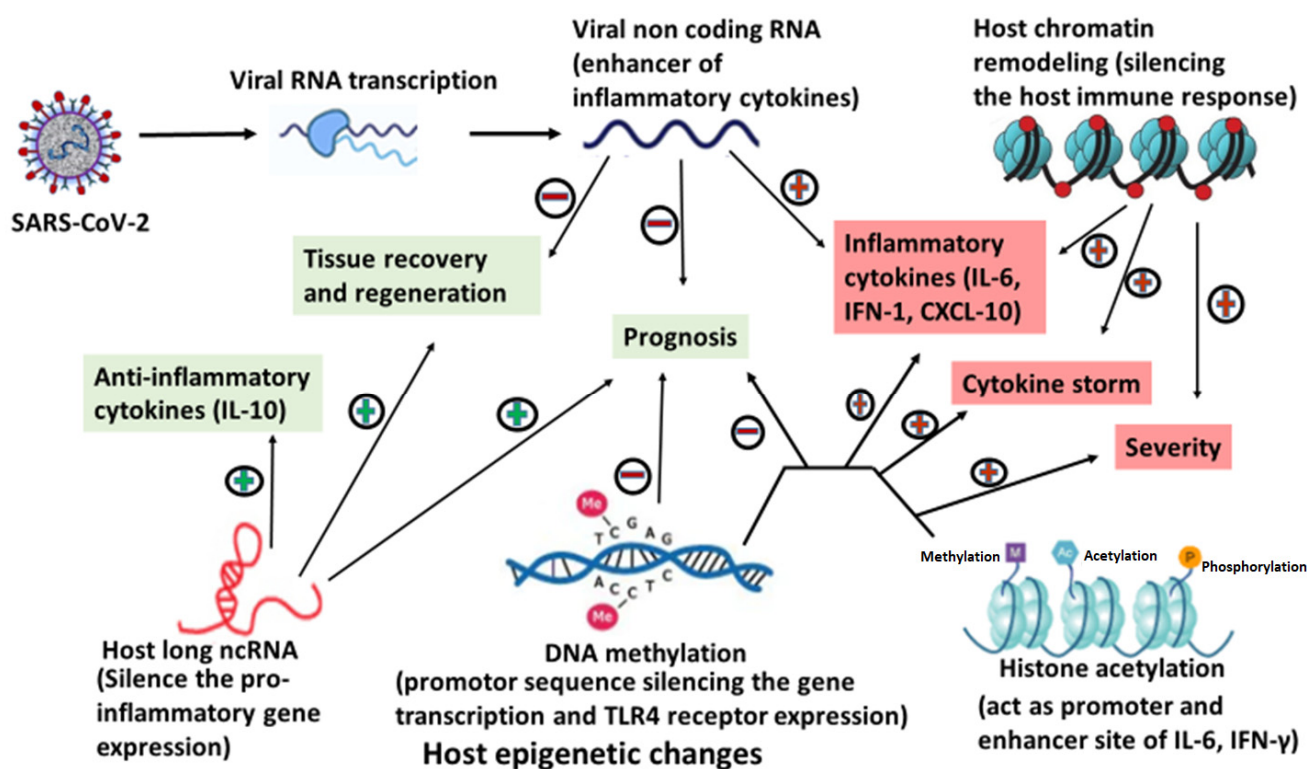


Figure 2. Schematic representation of roles of host epigenetic events and viral genomic RNA on the course of COVID-19 disease severity and prognosis of infection. Green-colored positive symbols represent a positive impact on the tissue repair process, red-colored positive symbols indicate increase adverse effects on infection state and disease severity, and red-colored negative symbols refer to adverse effects on prognosis.

4. Proinflammatory gene expression modified by histone assembly

In adaptive immunity, T cells are activated by antigen-presenting cells upon stimulation of inflammatory cytokines, which constitute epigenetic modification memory on CD4⁺ T and CD8⁺ T cells. Activated CD4⁺ T cells have high levels of H3K27me3 and H3Ac at the promoter and enhancer site of IL-6, IFN- γ , that this epigenetic regulation is maintained through memory CD8⁺ T cells, and permits a sudden, stronger, and quicker cytotoxic response to inflammation and additional antigen stimulation (Figure 2) [48,49]. Histone methylation plays a controversial role in the functions of macrophages against the inflammatory response. Activated macrophages can transform two functionally distinct phenotypes M1 and M2 in order to respond in an extracellular inflammatory status [23]. Activated M1 plays an initial role in host defense by producing pro-inflammatory cytokines interferon-gamma (IFN- γ), IL-6, and nitric oxide (NO) upon stimulation of lipopolysaccharide (LPS) [50]. M2 macrophages promote an anti-inflammatory profile (IL-10, IL-4) to resolve tissue injury, and tissue remodeling to control the immune response against infection [11]. Histone marks H3K9 methylation act as a regulatory factor for polarization of M2 from M1, blockage of conversion of trimethylated H3K27 (H3K27me3) to monomethylated H3K27 (H3K27me1) lead to blocking polarization of M2 from M1, resulting increase activation of M1 as well as the high rise of inflammatory cytokines IL-6, TNF-alpha, inflammation and irreversible tissue damage (Figure 2) [32,51].

On the other hand, the Histone lysine acetylation tail serves as an elongation and promotor site for the transcription of the inflammatory cytokine's gene [9]. A study also provides evidence that HDAC1 epigenetically acts as a silencer of anti-inflammatory cytokines expression in macrophages [49]. Acetylated histone forms the complex chromatin structure that inhibits the binding site for transcription activator and signal transducer (STAT3) at the promotor region of the IL10 gene which has a significant anti-inflammatory role in SARS-CoV-2 infections, resulting in the suppression of anti-inflammatory functions [49,52]. Different metabolites including short-chain fatty acids interfere the histone acetylation and induce the production of IL-10 and retinoic acids (RAs) by dendritic cells (DCs) as well as facilitating repair of injured tissue by releasing transforming growth factor (TGF- β) [41,53,54].

5. Epigenetic control on cytokines storms

The severity and mortality of COVID-19-infected patients have been linked to cytokines storm, which designate as a hyperactive immune response to exterminating the infectious agents and release of excess amounts of pro-inflammatory interleukins, interferons, chemokines, and tissue necrotic factors that are also caused injury to host cell [55]. Most of the COVID-19 cases are within a control limit that does not cause severe injury to host lung epithelial tissue, resulting in recovery without hospitalization and artificial respiratory support. However, several COVID-19 patients have undergone severe acute respiratory distress syndrome (ARDS) and fatal multi-organ failure due to hyperactive immune system induce cytokines production irreversibly leading to extensive pulmonary tissue damage. Radiographically, computed tomographic (CT) imaging of the chest displayed ground glass opacities over the area of the peripheral lung in severely ill patients [56]. In addition, postmortem lungs of patients who died from COVID-19 showed diffuse alveolar damage with edema, alveolar type-2 pneumocytes degeneration, hemorrhage, intra-alveolar fibrin deposition, alveolar

microthrombi and respiratory membrane disruption in histopathology and microscopic analysis [57,58]. So, what are the arguments that determine the consequences of COVID-19 infection in terms of severity and recovery with mild or no symptoms? There is a belief that host epigenetic adaptation plays a key role to modify the action of the host immune system against the COVID-19 virus. As a result, disease severity and recovery vary from person to person concerning age, race, sex, preexisting health condition, immune status, and exposure to environmental factors. A number of epigenetic studies have shown that exposure to commensals microbes or certain infectious agents with preexisting lung pathology can interfere with the epigenetic control of gene expression of host immune activation during COVID-19 infections and causes life-threatening conditions [32,59,60] because certain control of the epigenetic process is important to maintain the immune cell homeostasis, cell lineage stability, and cell fate decision.

Epigenetic processes including DNA methylation and histone modification could be also altered by viral infection. Most of the viruses in the coronavirus family are not enabled to deform the host cell genetic sequences, they are capable to utilize epigenetic machinery to invade the host immune system and manipulate the persistence of infection, host cell damage, transmission, and establishment of irreversible injury [61]. RNA viruses like the SARS-CoV-2 virus have a strong coalition with RNA modification. Noncoding RNA (ncRNA) is not directly involved in protein translation but enables the silence of the gene expression by blocking the mRNA translation [62]. Therefore, during viral infection, ncRNA can affect the chromatin looping structure along with DNA methylation that can interfere with the immune cell differentiation and reduce the expression of inflammatory IL-6, Interferon-gamma, and CCL5 mediators [63,64]. Pro-inflammatory cytokines IFN- γ , TNF- α , IL-1, and IL-6 are the key mediators of overwhelming inflammatory response and cytokine storm. Excess amounts of IL-6 and IFN- γ increase the incidence of shock, pulmonary edema, severe viral pneumonia, and hyperinflammatory alveolar damage as well as block the pathways critical to injury resolution [23]. Hospitalized patients with worsening COVID-19 symptoms show a rising level of pro-inflammatory IL-6, TNF, INF, and CCL5 which causes cytokine storm and severe ARDS. Experimental studies provide evidence that cytokine storms are most probably triggered by the amplifying factor of interleukin-6 associated with hyperactivation of the epigenetic machinery such as DNA methylation that facilitates the nuclear factor kappa B (NF- κ B) pathway and activates transducer of NF- κ B signaling and transcription 3 (STAT3) factors in order to impair resolution of inflammation in endothelial cells and alveolar epithelial cells [65,66]. Another fatal outcome of cytokines storm is coagulation abnormalities, patients with coagulation dysfunction may have a high risk of multi-organ involvement due to disseminated intravascular coagulation, hyperresponsiveness of coagulating factor with decreased thrombolytic function, and increased D-dimer [67]. As a consequence, there is a greater possibility of developing microthrombi of the lungs, heart, brain, liver, kidneys, and small vessels of limbs which is responsible for poor prognosis of infection with multiorgan failure [38].

6. Viral replication and transmission

After entering the host cell, the coronavirus executes its intracellular life cycle through replication and multiplication by expressing its genome to full functional RNA that are incorporated with glycosylated protein to release newly formed viral particles [14]. Viral gene expression is a complex process regulated by replication and transcription complex (RTC) after formatting

functional genome then initially elicited the formation of double-membrane vesicles (DMVs) in infected cell cytoplasm [8,9]. The coronavirus genome carries a considerably large number of single-stranded RNA genomes (size ranging from ~27 to 32 Kb) encompassed by cis containing 5' and 3' untranslated ends which are imperative regions for new RNA synthesis [9,14]. Viral replication organelles provide the protective microenvironment for the synthesis of sub-genomic mRNAs. Most of the cases, the virus utilizes ribosomal frameshifting to translate and express the polyproteins to create a suitable environment for RNA replication [6]. The viral replicase gene *rep1a*, *rep1b*, and two large open reading frames (ORF) express mainly *pp1a* and *pp1b* terminal polyprotein's [64]. The programmed ribosomal frameshifting changes the reading frame between *rep1a* and *rep1b*, resulting in the translation of polyprotein *pp1b*. Co-translationally non-structural proteins (nsps) are released from *pp1a* and *pp1b* upon proteolytic cleavage by using proteases (pro-papain-like proteases) [6]. The replicase *pp1a* and *pp1b* cleaved into *nsp1–11* and *nsp12–16* respectively which further assemble into the viral RTC (replication-transcriptase complex) to carry out the sub-genomic RNA replication [16]. Interestingly, each of *nsp1–16* maintains specific activities encoded for RNA replication fidelity such as *nsp1* blocks the innate immune response, *nsp13* encodes the RNA helicase domain, *nsp16* blocks viral RNA from MDA5 recognition [14]. Supporting function for RTC is carried out by *nsp1–11* including intracellular modulation, and co-factor production, whereas *nsp12–16* are considered to involve in viral RNA synthesis along with RNA modification and proofreading [59]. The viral sub-genomic RNA synthesis is initiated with the elongation of negative strand RNA which subsequently act as a template for positive genomic RNA strand extension. It is believed that *nsp12* contains RNA dependent RNA polymerase (RdRp) enzyme that switch the body transcription regulatory sequences (TRS) to leader TRS at the 5' end which leads to generating one sub genomic mRNA [3]. Consequent synthesis of mRNA, viral structural proteins S, E, M are translated to embed the endoplasmic reticulum (ER) membranes to travel through the ER to Golgi intermediate compartment (ERGIC). Therefore, the viral genome is encapsulated with N protein to form a new mature virion by budding into the membrane of the secretory compartment [9,10,16]. Following, mature virions exit out the infected cell by exocytosis and are capable to infecting the adjacent cell.

6.1. Epigenetic modification of coronavirus replication

Recent studies have discussed epitranscriptomic components that evolved to escalate viral transcription and replication in the host cell. These epitranscriptomic modifications are 2'-O-methylation of the ribose moiety of all four ribonucleosides (2'-O-MT activity) 5'-triphosphatase and helicase activity, N⁶-methyladenosine (m⁶ A), 5-methylcytidine (m⁵ C) and N⁴-acetylcytidine (ac⁴ C) and mainly regulate the functions of viral ncRNAs and called epitranscriptomic markers [23]. This epitranscriptomic modification provides protective support to viral components of RTC, the high presence of these factors acts as a safeguard for viral RNA from 5'-3' exonuclease activity in the course of host immune evasion like interferon response [9]. As a result, CoV-2 establishes the RTC to increase gene expression and ensure stable host cell infection in the process of weakening the host cell immune response against viral RNA by enhancing RNA stability [6]. RNA virus can also take advantage of an epigenetic silencing state during lytic replication in DNA virus-infected cells that may cause latent infection in a host cell. The capacity of viral gene expression depends on these epigenetic markers that promote RNA modification and

chromatin load to develop severe viral infection [16]. Recently, anti-viral drugs are evolved to target these markers to minimize the viral gene expression and bring down the severity of the disease. However, antiviral drugs like remdesivir show resistance to a high presence of N6-methyladenosine (m6 A), 5-methylcytidine (m5 C) and N4-acetylcytidine (ac4 C) and causing premature halt of viral termination [51]. So, there is a challenge to develop anti-viral agents that can prevent the expression of the epitranscriptomic factor and improve the outcome such as reduced severity of disease and mortality.

7. Evidence-based studies of epigenetic association on genomic influence in COVID-19 infection

A genome-wide association study (GWAS) revealed two genetic loci, Chr3p21.31 and Chr9q34.2 from samples of hospitalized COVID-19 patients with severe ARS by implementing a meta-analysis methodology on two case/control panels containing 835/1225 and 775/950 data from Italy and Spain [68]. They also found that the “A” blood type indicates a higher risk of COVID-19 infection whereas the “O” blood type shows a protective benefit among other blood types [68,69].

Significantly, certain empirical studies found Chr3p21.31 locus is associated with the constitution of the genomic machinery that facilitates severe coronavirus infection in the host cell. Furthermore, the Chr3p21.31 locus also causes severe disease in younger people (less than 60 years old) with less comorbidity, implying a de facto genomic link. Moreover, a study found a ~50 kb area of locus Chr3p21.31 as an allelic factor acquired from Neanderthals [70], approximately 50% of south Asian people and almost 16% of the European population have carried this type of genetic loci which were expected to be at risk of developing severe COVID-19 [68–71]. Epigenetic dysregulation has been linked to a higher risk of death in COVID-19 [72]. A study revealed that epigenetic alteration at the rs13015258C allele causes upregulation of CD26, which could explain the increased mortality rate among type 2 diabetes patients with SARS-CoV-2 infection [73]. Interestingly, several recent studies showed the association of vitamin D dysregulation and epigenetic aging in viral infection where the low level of molecular and cellular active form 1,25(OH)₂D (vitamin D) affects the epigenetic changes (modulated by histone acetylases and deacetylase) that impaired expression of the vitamin D-catabolizing enzyme CYP24 and increase the inflammatory gene expression of NF-κB [74]. Alteration of Vitamin D signaling pathways enhance the oxidative stress response and mitochondrial metalloproteinases gene polymorphism that accelerate the epigenetic aging with telomere attrition at the loci of 17q21.31, and 19q13.33 [75,76]. Markedly, vitamin D can influence immune cell proliferation through the overproduction of reactive oxygen species (ROS) and interfere the gene replication along with histone modification and DNA methylation.

8. Epigenetic influence on the systemic outcome

The pathophysiology of COVID-19’s systemic consequences is primarily unknown. Several experimental studies on rodents reveal epigenetic involvement in extrapulmonary manifestation, which identifies the severe systemic toxicity of SARS-CoV-2 where multiorgan involvement is more severe in rodents with compromised epigenetic factors [77–79]. Following those studies, the animals injected with the human ACE2 (hACE2) transgene followed by the SARS-CoV-2 virus showed less activity, a substantial reduction in body mass, and the sign of illness which reported devastating

phenotype where hACE2 transgene-carrying mice devoured almost 67% lesser food by weekly than those without this specific transgene for ACE2 receptor [77,80]. The resting heart rate of the treatment group (hACE2 transgene) was significantly lower than the control group, as shown by an electrocardiogram. Additionally, hACE2 transgene rodents displayed lower systolic and mean arterial blood pressures as measured with noninvasive methods. These experimental results have also provided evidence of splenic atrophy and leukocytosis with a significantly high number of granulocytes and a lower number of lymphocytes in the treated animals compared to the non-treatment group [79,80]. Based on prior lab findings, SARS-CoV-2 may be induced systemic toxicity in rodents that mirrors the clinical features of human infection including damage to several organ systems as neutrophilia and lymphopenia are crucial laboratory findings in over 80 percent of hospitalized patients with severe COVID-19 and is also one of the leading factors for poorer prognosis [79]. Recent research on individuals with COVID-19 has reported distinct patterns of T cell activation and also identified a relationship between severe disease and the inadequate or suboptimal response of immune T cells. Furthermore, a microscopic examination of postmortem tissue revealed prevalent histopathological changes in cardiac tissue with disruption of the myocardial tight junction and myofibrillar disarray, which can be one of the causes of death in COVID-19 disease. There is also evidence of SARS-CoV-2 causing reduced TCA cycle metabolites in human serum and epigenetic alteration of DNA methylation which impact gene expression related to immune activation and may play a role in COVID-19 pathogenesis [77]. Studies have shown that environmental variables (pollutants in the air), diet, and stress can all contribute to the development of gut dysbiosis/permeability [81], which in turn affects the immune system and the central inflammatory activity linked to SARS-CoV-2 [82] (Table 1). Gut dysbiosis is always associated with a decreased production of butyrate, a short-chain fatty acid produced by gut bacteria. Butyrate closes the gut through its actions on intestinal epithelial cells [83]. Butyrate can also pass intestinal epithelial cells and circulate in the bloodstream, where it has various effects, including a reduction in systemic immunity and the activity of glia in the central nervous system (CNS) [83]. Because butyrate inhibits histone deacetylase (HDAC), it is an effective epigenetic regulator and has mitochondria-optimizing effects [71,83]. In addition, the cytotoxicity of natural killer cells, which the body utilizes to fight cancer and viruses, can be increased by butyrate. Diabetes, obesity, cardiovascular disease (CVD), and respiratory disorders are related to a significant risk of death from COVID-19 infection because of gut dysbiosis [80] (Table 1). According to this, a “cytokine storm” caused by the initial viral infection may have increased gut dysbiosis and permeability, both of which could have contributed to the initial SARS-CoV-2 condition. In contrast, an increase in proinflammatory cytokines may have contributed to the development of the infection.

For SARS and MERS-CoV, the duration of activation of the type I interferons (IFNs) against viral particles is critical because the state of the disease also depends on the timing of immune cell response [79,84]. One of the many functions of interferon-stimulated genes is to govern the activation of the immune signaling cascade, which elicits the activation of a considerable amount of interferon-stimulated viral killings. Intracellular antiviral responses are mediated by interferons (IFNs) of types I, II, and III [85]. The Interferon family named IFNAR1 (p.Trp73Cys, p.Ser422Arg, p.Pro335del) and IFNAR2 (p.Glu140fs) variations were discovered from hospitalized COVID-19 patient serum with life-threatening pneumonia [76]. IFNAR1 and IFNAR2 are two subunits of IFNAR, activation loop of the self-enhancing positive feedback mechanism is triggered by the binding of type I interferon (IFN) to the type I interferon receptor in the process of immune attack against the virus.

Reduction of adaptive host immune response, persistent viral invasion, and clearance of viral presence were linked to IL6 polymorphisms that were either low or high generating gene expression [86–88]. A rising amount of pro-inflammatory cytokines, immune system dysregulation, and the formation of micro thrombosis are all characteristics shared by severe COVID-19 patients (Table 1). This is most likely the result of an increase in angiotensin II levels generated by the SARS-CoV-2 and a link between inflammation caused by oxidative stress, and more ACE2 interaction with viruses found in COVID-19 patients, which contributes to devastated loss of cell function [89]. 22.2 million genetic variations were studied in 332 COVID-19 patients across five states of severity (asymptomatic, mild, moderate, severe, and critical life-threatening). The most significant gene locus related to severity was TMEM189–UBE2V1, part of the IL1 signaling pathway [90].

Table 1. Factors associated with epigenetic changes play an important role in COVID-19 pathogenesis and disease outcome.

Factors induced epigenetic modification	Impact on the mechanism of disease formation	Functional outcome of COVID-19 infection	References
Age	Biological aging may affect the metabolic process of DNA methylation and regulation of angiotensin converting enzyme 2 (ACE2) which facilitate the COVID-19 infection.	Leading to severe COVID-19 disease and hospitalization with increased mortality.	[91]
Sex	X chromosome in women act as an enhancer of some immune regulatory genes like toll-like receptor (TLR) and decrease the viral load due to the circulating concentration of ACE2 being lower in female than male.	Females have been shown more resistant to COVID-19 and suppress the viral mechanisms and immunoinflammatory reaction toward cytokine storms.	[92]
Race and Ethnicity	Several studies have provided evidence of racial disparities in risk and death related to COVID-19 disease. Black, Native American and Hispanic people have experienced worsening COVID-19 symptoms with higher systemic complications compared to white people.	The cause of racial disparities in disease outcomes is still unknown but it may be resulting from poor SES, low vaccination rate, or genetic variation.	[93,94]
Diet and nutrition	Poor diet quality is one of the socioeconomic burdens that weaken the immune and metabolic support.	Healthy and balanced diets provide a stable immune system and indirectly may have a role to lower the risk and severity of COVID-19 disease.	[95,96]
Obesity	Obesity may have an adverse impact on strength of the immune system (more prone to inflammation) and reduce respiratory ventilation by reducing lung capacity.	Obesity is one of the inducing factors for severe COVID-19 infection and is also responsible for prolonged hospitalization with multiple systemic complications and death.	[97,98]
Stress	Upregulated the viral transmembrane serine protease 2 (TMPRSS2) and transcriptomic viral RNA factors by reducing the host viral resistance	ACE2 expression is increased under conditions of cell stress and hypoxic conditions. Increase susceptibility to COVID-19 infection.	[28]

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Factors induced epigenetic modification	Impact on the mechanism of disease formation	Functional outcome of COVID-19 infection	References
Oxidative response	Overproduction of toxic ROS can lead to cytokine storm and alter the host immune system.	Inflammatory lung damage and block treatment against hyperinflammation.	[99]
Viral load	A number of researchers have found worse outcomes with high viral exposure, which can be a determinant factor for COVID-19 outcome and prognosis.	There is also a controversy about the relationship between viral load and disease severity. Argyropoulos et al. have provided no significant connection between viral load and severity of infection.	[28,31,35]
Variants of SARS-CoV-2	Omicron strain (BA.1) and its subvariants are more contagious but less severe than delta variants.	Compared to the infection of patients with alpha, delta, beta and omicron variants, delta is more associated with hospitalization and decreased overall survival.	[31,100]
Host immunity	Immunodeficiency patients have difficulties maintaining the innate immune system due to a lack of interferon regulatory factors and toll-like receptors signaling against viral infection.	Immunodeficiency may lead to higher susceptibility to severe COVID-19 infection and death.	[101]
Infection	Existing bacterial infection like pneumococcal or E.coli infection is one the risk factor to accelerate the disease severity.	Increased risk of acute infection and mortality among patients with these infections.	[102]
Preexisting conditions	Chronic disorders like diabetes, hypertension, and lung and liver disease alter the metabolic pathway in immune cells that are required for activation, differentiation, and function of immune cells against viral infection.	Host immune signaling pathways are operating by fuels from metabolites, so preexisting diseases may change a large number of gene expressions and cytokines production that leads to increased susceptibility to viral infection.	[102,103]
Substance use disorder	Chronic use of opioids or stimulant drugs weakens the immune system and is one of the causes of failure to rapidly respond to infection.	Fatal drug overdose increases the risk of having serious COVID-19 illness compared to patients without SUD.	[104]
Smoking	Nicotine acts as an immunosuppressant and induces the epigenetic modification of bronchial epithelium as well as decreases the neutrophilic phagocytic activity that also affects cell signaling and ROS production.	Increase the transmission risk and severity of COVID-19 illness, also promote upregulation of pulmonary ACE2 receptor expression.	[105,106]
Alcoholism	Alcohol triggers the release of pro-inflammatory cytokines and alters the interleukin-mediated microglial activation that leads to neuroinflammation and BBB dysfunction. So, it may facilitate the presence of the virus in CNS and evoke a serious cytokine storm inside the brain.	Patients with alcohol use disorder have greater vulnerability to severe COVID-19 infection with a concurrence risk of neuropsychiatric complications and other medical co-morbidities.	[106–108]

9. Importance of epigenetic implication in the management of COVID-19 infection

In order to contribute to viral epigenetic therapeutics, it is necessary to understand the fundamental elements of the epigenetic process that regulates the gene expression of the immune system. Usually, epi drugs work on gene regulatory networks, and changes in gene expression towards pathological outcomes and produce risk from the systemic effect of such therapies. Because epigenetic mechanisms play a significant role in controlling several facets of COVID-19, epigenetic enzymes could be used as a potential therapeutic target. For the treatment of COVID-19, several clinical trials have focused on epigenetic pathways, and many more are now underway. According to various empirical studies, trained immunity (TRIM) is an epigenetic memory that immune cells have for primary infection by epigenetic reprogramming [109,110]. The primary infection/exposure allows innate immune cells to build an epigenetic memory for the pathogen and induce a more robust immune response to the second exposure. It was discovered in a study that β -glucan-driven TRIM results in epigenetic reprogramming and can be used to treat COVID-19. For COVID-19 treatment, RNA-based molecular therapeutic techniques have also been proposed. RNA-based molecular therapy methods epigenetically modulate the genes essential for viral entry, replication, and maturation. MicroRNAs (miRNAs), small interfering RNAs (siRNAs), and locked nucleic acid antisense oligonucleotides (LNAs) targeting the spike protein's 5'UTR sections are thought to be helpful in both preventing and treating COVID-19 infection [111]. A recent study discovered a link between the crucial COVID-19 gene and the intron mutation rs2236757 of the IFNAR2 gene [70]. To transmit IFN-activated phosphorylation signals, IFN receptors use cytoplasmic kinases like tyrosine kinase 2 (TYK2) [112] where rs74956615 was linked to crucial COVID-19 near the TYK2 coding locus, and TYK2 was proposed as a potential therapeutic target [70]. Immunosuppressive drug (dexamethasone) an effective corticosteroid, was found to attenuate the cytokine storm syndrome in COVID-19 patients with lower mortality rates. In individuals with hyperinflammation after SARS-CoV-2 infection, the IL-1 inhibitor anakinra and the IL-6 receptor inhibitor tocilizumab showed a significant survival advantage. IFN inhibitors reduce SARS-CoV-2-induced systemic inflammation; however, the duration of action of IFN antagonism therapy is important since it determines the outcome of infection. IFN-receptor antagonists prevented inflammatory responses and facilitate the slow-down of adverse progress of SARS-CoV, although IFN neutralization reduced IFN production. TNF promoter can bind with H3K9 histone methyltransferase G9a and DNA methylase DNMT3a/b enzymes to activate the histone modification and DNA methylation respectively, resulting in the transcriptionally restrictive state of the TNF promoter and reduce TNF- α protein concentration. Histone acetylation (H3K9ac, H3K36ac, and H4K5ac) may reduce the production of IL-8 and TNF- α levels which primarily increase in response to COVID-19 infection. Trichostatin A (TSA) is a potent broad-spectrum histone deacetylase inhibitor (HDACi), was used to reduce the synthesis of these proinflammatory mediators [113].

10. Conclusions

This discussion establishes the evidence of epigenetic alteration in COVID-19 pathogenesis that reforms the host immune response to contagion and is also a responsible factor for worsening the disease outcome associated with deadly multisystem involvement. Consequently, hospitalization and severity of infection vary among the population due to their adaptive epigenetic mechanism towards regulating cytokine storm-mediated inflammation and cell restoration for recovery. Epigenetic

therapies are a demanding field of research in comparison with existing conventional treatments for coronavirus disease, due to their potential therapeutic targets to specific mechanisms to block the disease progression. Therefore, this study strengthens the understanding of epigenetic involvement in COVID-19 disease progression by outlining the potential therapeutic and preventive approaches to reduce hospitalization and further systemic impairment.

Conflict of interest

The authors declare no conflict of interest.

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