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Understanding the epigenetic mechanisms in SARS CoV-2 infection and potential therapeutic approaches

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ABSTRACT

COVID-19 pandemic caused by the Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) has inflicted a global health challenge. Although the overwhelming escalation of mortality seen during the initial phase of the pandemic has reduced, emerging variants of SARS-CoV-2 continue to impact communities worldwide. Several studies have highlighted the association of gene specific epigenetic modifications in host cells with the pathogenesis and severity of the disease. Therefore, alongside the investigations into the virology and pathogenesis of SARS-CoV-2 infection, understanding the epigenetic mechanisms related to the disease is crucial for the rational design of effective targeted therapies. Here, we discuss the interaction of SARS-CoV-2 with the various epigenetic regulators and their subsequent contribution to the risk of disease severity and dysfunctional immune responses. Finally, we also highlight the use of epigenetically targeted drugs for the potential therapeutic interventions capable of eliminating viral infection and/or build effective immunity against it.

1. Introduction

In the year 2020, we have witnessed a formidable global health crisis, coronavirus disease 2019 (COVID-19) which had emerged from Wuhan (Hubei, China) in late 2019 and left no one unscathed across the globe. With no 'silver bullets' available for the treatment, the novel respiratory viral pathogen severe acute respiratory syndrome coronavirus (SARS-CoV-2), the causative agent of COVID-19 has led to heavy mortality, and although the initial overwhelming wave of infections subsided the pandemic continues to run its course: more than 6.3 million deaths have been registered as of 15.06.2022 (COVID-19 Map - Johns Hopkins Coronavirus Resource Center, 2021). However, within less than a few months after the beginning of the COVID-19 pandemic, several research teams rose to this catastrophic challenge and embarked on a historically unprecedented race for the development of vaccines against it. Today, millions are pinning their hopes on the multiple vaccination programs which have already been rolled out in several countries (COVID-19 vaccine tracker and landscape, 2022, Le et al., 2020, Deplanque and Launay, 2021). Although the flurry of results from the clinical trials of COVID-19 vaccines positively indicated that the successful implementation of these vaccination programs may lead to the end of the pandemic and return of the pre-pandemic normalcy, questions of the efficacy of these vaccines in terms of their potential to eradicate SARS-CoV-2 infection remain (Juthani et al., 2021). What if the vaccines safeguard immunized individuals from reinfection but do not prevent them from infecting others? Thus it could actually worsen the pandemic if vaccinated individuals remain apparently healthy but become asymptomatic carriers. Moreover, there are still chances of newer infections or even reinfections following vaccination until a level of protective population-level or 'herd' immunity is achieved. In addition to these uncertainties, the latest emergence of newer variants of coronavirus like omicron and BA.2 harboring mutations that supposedly enable them to transmit more rapidly and evade the immune system has raised a pressing concern about the effectiveness of the present vaccines against them (Callaway, 2021). Despite a large section of world's population is partially or fully vaccinated at present, the latest omicron variant of coronavirus, is wreaking havoc, although symptoms are milder than earlier variants. This indicates that these vaccines alone will likely not be sufficient to end the pandemic. Therefore, small molecule drugs, owing to their capability of reducing morbidity and mortality are believed to be still necessary to fight the SARS-CoV-2 infection or yet another future pandemic coronaviruses. Indeed, a large number of drugs including remdesivir, favivirapir, antimalarial hydroxychloroquine, serine protease inhibitor like camostat mesylate, anti-interleukin (IL) 6

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therapy with tocilizumab (humanized monoclonal antibody against the IL-6 receptor), or conventional broad-range corticosteroids like dexamethasone have entered clinical trials to assess their potential against the SARS-CoV-2 infection but either failed to generate a significant response or had been ruled out owing to insufficient evidence (Shaffer, 2020). Although developing the direct acting antivirals is still of the highest priority, chances are there that like in the case of vaccines, emerging variants of SARS-CoV-2 and other viruses with pandemic potential may render treatment with these drugs either less effective or even completely ineffective. Therefore, amidst the hour of present challenge and also for future pandemic preparedness, besides targeting viral components, emphasis should also be given to develop novel therapeutics that act in a host-directed manner and are capable of inducing sustained or long-term defense against at least all the strains of a particular family of viruses including coronavirus, if not all family of viruses which may be a bridge too far.

In such a scenario, epigenetic modifications on specific genes of host cells, specifically immune cells represent attractive and therapeutically relevant targets. Studies have already shown how these modifications play pivotal roles in governing the functions of various immune cells during their journey from a naïve state to an activated state in response to any pathogenic insults (Busslinger and Tarakhovsky, 2014; Placek et al., 2019). Emerging reports suggested how SARS-CoV-2 influences the epigenomic landscape of the host immune cells which in turn governs the outcome of the immune response against it. As epigenetic modifications are reversible phenomena, drugs targeting the mediators involved in the corresponding pathways of these modifications can be used to restore and/or improve immune recognition and immunogenicity. Studies have already shown the possible beneficial roles of several epigenetic drugs (Epidrugs) as immunomodulatory agents during cancer immunotherapy (Dunn and Rao, 2017; Villanueva et al., 2020). Although much remains to be investigated, potential insights from the emerging reports on SARS-CoV-2 infection and parallels drawn from the inferences of previous studies on other human coronaviruses (HCoV) infections may lead to the identification of valuable epigenetic targets that can help design newer therapeutic strategies effective for different types of subjects and different stages of the disease. Although, the vaccine will remain the mainstay of therapy against SARS-CoV-2, co-administering the epidrugs may help in fighting the virus by strengthening the immune response, thus boosting the efficacy of vaccines. Moreover, epidrugs can be used to elicit the antiviral T cell memory which will further help to prolong the effect of immune defense against coronavirus infection.

This review will address some fundamental issues on how SARS-CoV-2 infection may influence the epigenetic mechanisms of the host and discuss what promising druggable epigenetic targets can be exploited for successful therapeutic intervention. Can epigenetic mechanisms be targeted for the conversion of exhausted T cells into antigen specific functional memory T cells? In addition, this review will also address comprehensively how epigenetic manipulation can be utilized to augment vaccine efficacy or as adjuvant therapy.

2. Pathogenesis of SARS-CoV-2

2.1. Viral entry and role of innate immunity

SARS-CoV-2 is a single stranded RNA virus of *Betacoronavirus* genus in the *Coronaviridae* family. The viral envelope contains spike-proteins (S protein) which via interacting with the host cell receptor angiotensin converting enzyme 2 (ACE2) mediates the entry of the virus into host cells (Wang et al., 2020). ACE2 is expressed in various cells of the lungs (airway epithelial cells, alveolar pneumocytes, alveolar endothelial cells, and lung macrophages), kidneys (renal epithelial cells), and small intestine (enterocytes). Following binding with the ACE2 receptor and subsequent priming of the S protein (activation induced cleavage of S protein) by host proteases such as furin and transmembrane serine protease 2 (TMPRSS2), the fusion of the virus with the host membrane takes place (Hoffmann et al., 2020). Upon entering the host cytoplasm, the virus delivers its RNA which undergoes replication and viral proteins are being synthesized. Newly synthesized viral RNA and proteins get assembled into new virus particles which then get released from the host cells and infect other cells. As in the case of other RNA viruses, the antiviral immune response against SARS-CoV-2 typically arises, via recognition of viral single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA) by pattern recognition receptors (PRRs) like cytosolic RIG-I like receptors (RLRs) and extracellular or endosomal Toll-like receptors (TLRs). PRR activation leads to the secretion of various pro-inflammatory cytokines including IL-1, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α), and most importantly, type I/III interferons (IFN) (Vabret et al., 2020). As a part of this initial and localized inflammatory response, resident innate immune cells and virus-specific T cells become activated and accumulate near the sites of infection and try to eliminate the virus-infected host cells, thus limiting the spread of the virus. Most individuals with a potent immune system can constitute such an early activation of the innate and adaptive immune response against the virus and are thus able to recover from the disease once the immune cells clear the viral burden. However, the systemic spreading of highly pathogenic viral infection originates as the primary immune barrier breaks apart. Studies revealed that SARS-CoV-2 antagonizes the initial antiviral innate immunity, via several mechanisms like evading the PRR sensing, and most importantly, inhibiting the IFN-I/III induction (Blanco-Melo et al., 2020). Indeed, patients with severe clinical symptoms of COVID-19 predominantly showed extremely low plasma level of IFN-I, implying a higher degree of impairment of the IFN-I signaling program in them as compared to moderate and healthy subjects (Park and Iwasaki, 2020; Hadjadj et al., 2020). Suppression of antiviral IFN-I/III signaling provides the virus substantial window of time to proliferate and spread the infection inside the pneumocytes and alveolar cells leading to large influx of monocytes, macrophages, followed by T cells. In an attempt to thwart the viral infection further, all these immune cells become frantically active and secret a profuse amount of pro-inflammatory cytokines, a phenomenon clinically termed as “cytokine storm” (Mangalmurti and Hunter, 2020). Several comprehensive analyses on the immune response of COVID-19 infections have shown an increased circulating concentration of pro-inflammatory cytokines, such as IL-6, TNF-α, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α (MIP1α), and chemokine (C-X-C motif) ligand (CXCL) 10 in case of severe infections as compared to mild infections (Merad and Martin, 2020). In addition, the plasma levels of multiple inflammatory chemokines including CXCL17, CXCL8, CXCL1, CXCL2, CCL1, and CCL2 have also been found elevated (Vabret et al., 2020; Merad and Martin, 2020; Zhou et al., 2020). Cytokine storm may also be generated from the infection induced gut dysbiosis- an imbalance of gut microbial flora which further exacerbates lung pathophysiology. Several reports have discussed a crucial role of crosstalk along the gut-lung axis. Loss of gut microbial diversity contributes to the lack of production of various anti-inflammatory metabolites like short chain fatty acids (SCFAs) (for ex: butyrate and acetate) which could otherwise play some role in subduing hyperinflammation (Rishi et al., 2020). Indeed, higher proportions of pro-inflammatory macrophages and neutrophils have also been observed in the bronchoalveolar lavage fluid (BALF) of COVID-19 patients with severe symptoms compared with those exhibiting mild symptoms (Liao et al., 2020). All these cytokines and chemokines significantly contribute to the arousal of lung pathology by recruiting more monocytes and neutrophils to infected tissues of lungs which further aggravate the local inflammation induced damages, thus promoting the disease severity and risk of mortality. Along with this, COVID-19 patients show an increased level of neutrophil extracellular traps (NETs) in their plasma, lung epithelium, and tracheal aspirate as compared to healthy controls (Zuo et al., 2020). NETs are the extracellular complex of DNA, histones, microbicidal proteins, and oxidant enzymes (myeloperoxidase, nitric oxide synthase, and NADPH oxidase)

released by the dying neutrophils to restrict infections; however, when not properly regulated, NETs can initiate and propagate inflammation and thrombosis. There is emerging evidence to implicate inflammatory cytokines, such as IL-1β and IL-6 enhance the production of NETs through a positive feedback loop, thereby aggravating lung tissue damage (Tsourouktsoglou et al., 2020). In patients like older individuals with the weaker immune system, SARS-CoV-2 has been found to trigger such aberrant immune responses which subsequently lead to the development of severe clinical manifestations of the disease- essentially characterized by acute respiratory distress syndrome (ARDS) with fatal respiratory failure (Vabret et al., 2020). Notably, the severe COVID19 patients also showed functional impairment of plasmacytoid dendritic cells (pDCs) and monocytes and reduced HLA-DR. expression on them, indicating that these cells are incapable of presenting viral antigens to T cells (Arunachalam et al., 2020). Taken together, these data suggest that while the attenuated IFN-I signaling helps the virus to evade the primary innate immune defense of the host, the incapacitated monocytes and mDCs (myeloid derived DCs) thus indicate the suppression of innate immune system and inadequate triggering of antigen-specific T cell activation which further provides the virus a favorable niche to dwell and perpetuate the infection. As a result, hyperinflammation persists, tissue damage in lungs and other vascular organs is continued.

2.2. T cell immunity

Along with innate immunity, SARS-CoV-2 throws our adaptive immune system out of kilter also. An unusually severe lymphopenia, characterized by a lack of major T cell population (CD4+ and CD8+), B cells, and natural killer (NK) cells indicate that adaptive immune response almost completely collapses. A drastic loss of regulatory T cells (Tregs) population, a class of T cells specialized in suppressing inflammation by reducing the proliferation of activated T cells and inhibiting inflammatory cytokines further aggravates tissue inflammation (Qin et al., 2020). Moreover, elevated exhaustion levels and reduced functional diversity of T cells are other characteristic phenomena that also have been correlated to the disease progression and severity. Therefore, it is reasonable to speculate that loss of T cells might aggravate certain pathological inflammatory responses associated with SARS-CoV-2 infection, sustaining a dysregulated T cell-cytokine loop whereas pathogenic T cells themselves can contribute to the rise of the systemic concentrations of pro-inflammatory cytokines (de Candia et al., 2021). Taking all these accounts into considerations, it can be understood that with an impaired innate as well as adaptive immunity, COVID-19 causes excessive tissue damage in lungs and other vascular organs via 'cytokine misfiring' or hyperinflammation. However, more studies are required to obtain a greater horizon about the pathogenesis of this highly devastating disease.

3. Epigenetic modifications and SARS-CoV-2 infection

Epigenetic modifications, as originally defined, are heritable covalent changes to DNA that alter the gene expression without any changes in the underlying nucleotide sequence. However, currently, a more modern definition of these modifications has been encompassing a broader range of phenomena also including transient changes in chromatin structure and post-transcriptional modifications by non-coding RNAs (ncRNAs). Epigenetic modifications are crucial mechanisms through which the host genome integrates intrinsic and environmental signals and thus governs the cells "to register, signal or perpetuate altered activity state". There are mainly three fundamental mechanisms through which these modifications occur, including DNA methylation, post-translational histone modifications, and the functions of ncRNAs (both long ncRNA or lncRNA and microRNA or miRNA). Each of these mechanisms is not an isolated event, rather works in close ties with others, thus creating a complex web of intricately controlled cellular signaling batteries which ultimately govern the infection outcome.

Several emerging reports have now offered direct evidence of the epigenetic modifications of various host genes during SARS-CoV-2 infections. Different epigenetic mechanisms associated with the role of various risk factors including age, sex, and other comorbidities have been shown to also influence fatality and poor clinical outcomes in COVID-19. Khan et al. (2020) has identified 10 epigenetic factors that were deregulated: DTX3L, HDAC7, HDGF, PRDM1 PRMT1, and TRIM16—upregulated, and FOXO1, HELLS, PADI3, and PPARGC1A—downregulated (Khan and Islam, 2021).

In the following sections, we will elaborate on the epigenetic dysregulation of the expression of critically important genes, mostly *ACE2* and other immune regulatory genes associated with various pathological manifestations of COVID-19 (Fig. 1).

3.1. Epigenetic regulation of ACE2 expression and risk of COVID-19

As ACE2 receptor plays significant roles in mediating the entry of the virus into the host cells, it can be understood that the epigenetic signature of *ACE2* gene predominantly controls the initial step of entry and fusion of the virus. Several studies have shown how ACE2 expression is differentially regulated in various tissues by epigenetic mechanisms that further impact the infection outcome. Du et al. (2022) reported that differential expression of host receptors including ACE2 and TMPRSS2 depends on the tissue and cell-specific chromatin accessibility at their promoter which explains the tropism of SARS-CoV-2 virus inside our body. Assay for transposase-accessible chromatin coupled with high-throughput sequencing (ATAC-seq) performed in this study revealed the promoter of ACE2 is accessible in the lungs, intestines, and placentas and in basal cells, ciliated cells, club cells, alveolar type 1 (AT1) cells and alveolar type 2 (AT2) cells of lungs. The genome-wide ChIP-seq analysis and DNA methylation array revealed the variable degree of DNA methylation of the ACE2 gene in different tissue subtypes, lowest methylation across three CpG sites (cg04013915, cg08559914, cg03536816) of *ACE2* gene being observed in lung epithelial cells compared with other tissues (Corley and Ndhlovu, 2020). Subsequent studies have shown variable ACE2 DNA methylation signatures of human lung tissues in both men and women. *ACE2* locus in females was found significantly hypomethylated as compared with males (Corley and Ndhlovu, 2020) which denotes the higher expression of ACE2 in them. Females have other mechanisms like escaping X-chromosome inactivation (XCI) through which they achieve altered ACE2 expression. XCI is an epigenetic gene regulation mechanism jointly controlled by non-coding RNA, DNA methylation, and histone modification, responsible for dosage compensation or equalizing the expression of X-linked genes between sexes. However, ~30% of X-linked genes escape XCI and are expressed from both X chromosomes in females. Researchers have found that the *ACE2* gene is located on the X chromosome and by escaping the XCI, becomes upregulated in females. Thus men are hemizygous, as they have only one copy of chromosome X while women are heterozygous for *ACE2* (Gemmati et al., 2020). Despite the infection rates being almost similar for both males and females, higher ACE2 expression has been correlated to lower susceptibility to severe forms of COVID-19 and more protection in females. However, considering that sex hormones also regulate the function of ACE2, it is difficult to determine the real effect of XCI on the severity of COVID-19 only through ACE2 expression at this stage. Another previous evidence highlighted hypomethylation mediated overexpression of ACE2 and its association with the onset of severity in the systemic lupus erythematosus (SLE) patients upon infection of SARS-CoV-2 in peripheral blood T cells (Sawalha et al., 2020). The author showed that demethylation of IFN-regulated genes, NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), and key cytokine genes in T lymphocytes of SLE patients might aggravate the immune response to SARS-CoV-2 and increase the likelihood of cytokine storm. Besides DNA methylation, the *ACE2* locus is also rich in epigenetic regulation marks of histone acetylation and methylation (Chen et al., 2020). Transcriptomic analysis and

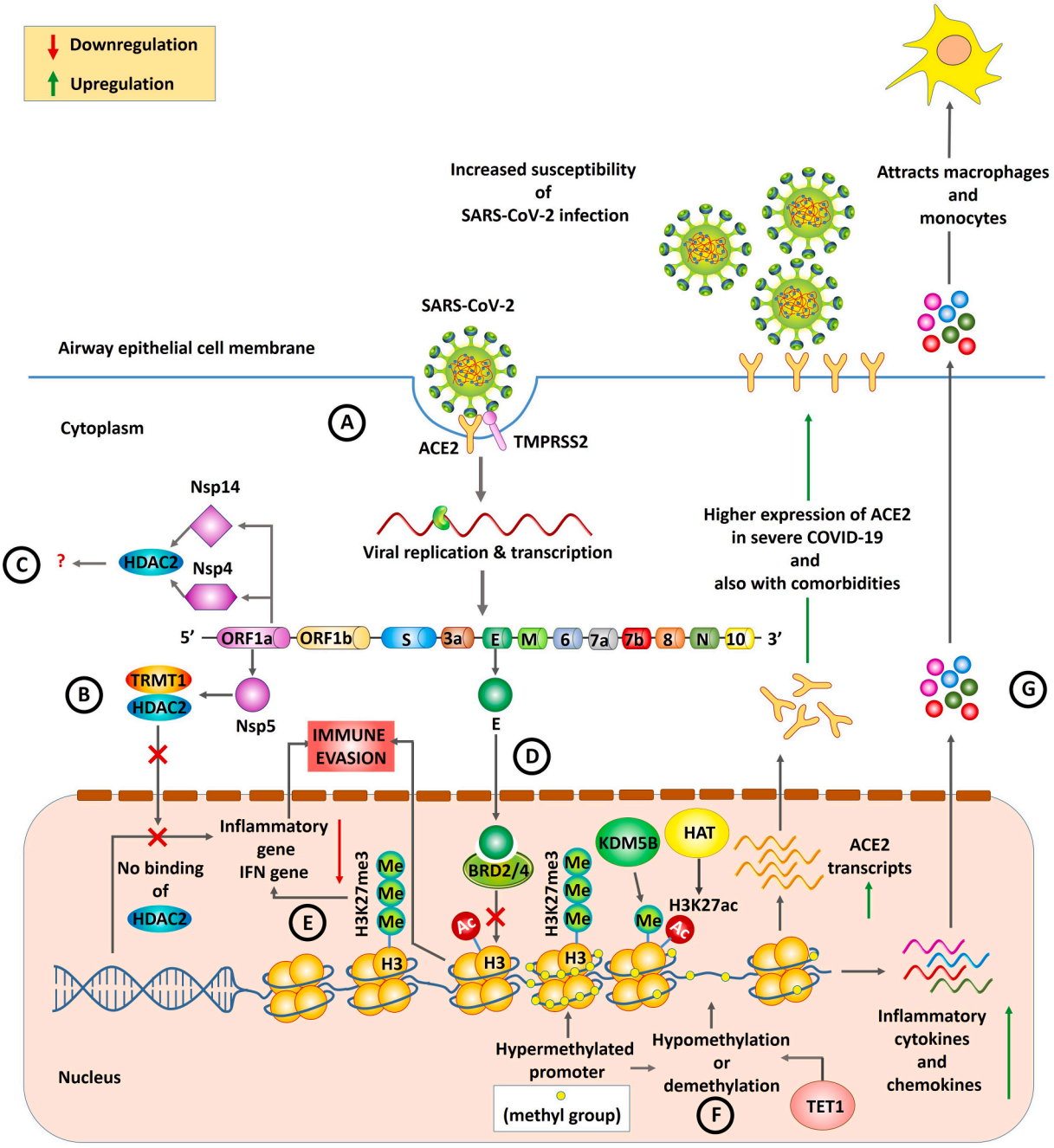

Fig. 1. Interaction of SARS-CoV-2 with various host epigenetic factors (A) SARS-CoV-2 enters the host cells via binding to ACE2 receptor. Following internalization, the viral genome is released into the host cytoplasm and gets transcribed by a combination of host factors and virus encoded protein complex. SARS-CoV-2 has the largest genome among all the coronavirus known to date, comprising of ~29 kb in length which includes 14 open reading frames (ORF) encoding both structural and non-structural proteins. (B) ORF1a encodes Nsp5 which interacts with HDAC2 and prevents its entry into the nucleus. (C) Nsp4 and NSp14, both encoded by ORF1a also interact HDAC2, although the downstream signaling is not known. (D) Viral transmembrane protein, 'E' interacts with BRD2/4, members of BET domain family of epigenetic readers, thus disrupting the BRD-acetylated histone interaction, modulating the protein expression beneficial to the virus. (E) SARS-CoV-2 infection also causes repressive histone modifications like H3K27me3 on innate immune response genes which help in their immune evasion. (F) Epigenetic regulation of ACE2 expression is crucial for the spread of SARS-CoV-2 infection as higher expression of ACE2 is correlated to greater infection risk. SARS-CoV-2 may promote DNA hypomethylation in the ACE promoter by TET1, KDM5B, and acetylation by HAT which results in enhanced transcription of ACE2 and promote the chance of infection. (G) DNA hypomethylation and active chromatin modification of inflammatory genes lead to their overexpression which further attract macrophages and monocytes to the site of infection. Large influx of innate immune cells exacerbates tissue inflammation and damages. [ACE2: Angiotensin converting enzyme 2; BRD2/4: Bromodomain containing 2/4; HAT: Histone acetylase; HDAC: Histone deacetylase; H3K27ac: Histone 3 lysine (K) 27 acetylation; IFN: Interferon; KDM5B: Lysine (K) demethylase; Nsp: Non-structural protein; ORF: Open reading frame; TRMT1: tRNA methyltransferase 1; TET1: Ten-eleven translocation methylcytosine dioxygenase 1; TMPRSS2: Transmembrane serine protease 2; Ac: Acetyl; Me: Methyl].

systems biology approaches revealed the upregulation of several genes related to histone modifications including *HAT1*(histone acetyl transferase 1), *HDAC2* (histone deacetylase 2), and *KDM5B* (lysine specific demethylase 5B, also known as *JARID1B*) in severe COVID19 patients with comorbidities which are also positively associated with ACE2 expression (Pinto et al., 2020). In addition, the authors have identified specific histone acetylation (H3K27ac) and histone methylation (H3K4me1 and H3K4me3) in the *ACE2* locus of human lungs. Finally, the study concluded that ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. Moreover, silent information regulator T1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+) dependent class III HDAC, has been shown to play a crucial role in regulating the ACE2 expression by binding to its promoter (Clarke et al., 2014). Numerous studies have reported that HDAC inhibitors downregulate the ACE2 expression, indicating an important role of histone deacetylation in the regulation of ACE2 function.

Despite extensive evidence, the literature is still scanty about the COVID-19 ACE2 epigenetic pattern and the association of the level of ACE2 expression with the severity of the SARS-CoV-2 infection is also obscure as reflected by several counterintuitive reports. Children have shown lower fatality from COVID-19 and better prognosis than older individuals but several studies have reported that ACE2 level decreases with age i.e. children have higher expression of ACE2 as compared to the older individual. How can ACE2 reduction in older individuals and patients with other comorbidities like cardiovascular-risk put them at greater risk of COVID-19 severe symptoms when ACE2 is the entry-point for the disease into the host cells? On the contrary, substantial evidence is pouring in recently which showed the increase of ACE2 expression with age which makes the correlation between the age-wise variation of ACE2 level and susceptibility to severe COVID-19 more confounding. However, these recent reports can be supported by the age-wise hypomethylation of ACE2 promoter as hypomethylation increases the expression of ACE2. In addition to the ACE2 expression, aging also governs the functions of other physiological systems like immune response which further determines the course of disease pathogenesis. A dedicated section (Section 3.6) on the effects of aging on the clinical outcome of COVID-19 will elaborate further on how various age associated epigenetic changes can be implicated to influence disease severity in older patients. Similar to the children, females, despite having a higher level of ACE2 expression, also show lesser susceptibility to the disease severity in comparison to males. Thus from this proposition, the pattern of the male preponderance of COVID-19 fatality cannot be explained and the possible association of ACE2 expression and sex cannot be determined. Therefore, categorically the dilemma about the ACE2 expression, whether it is harmful or beneficial for COVID-19 severity remains. Accordingly, the role of various epigenetic mechanisms involved in the regulation of ACE2 expression is not yet clearly established. Although some studies have linked higher ACE2 expression with better prognosis (as in females) probably via maintaining angiotensin1–7 levels that counteract the pro-inflammatory actions of angiotensin2 (Ang II), there are no data so far reporting the expression levels of ACE2 and Ang II in COVID-19 patients. Moreover, the entry of SARS-CoV-2 into cells through membrane fusion markedly downregulates ACE2 receptors (Verdecchia et al., 2020). Whether this downregulation involves ACE2 DNA methylation alterations needs to be explored. Altogether, it can be understood that ACE2 is much more than just a receptor for SARS-CoV-2 entry and have other versatile physiological roles. More studies are still required to explore those roles in connection to COVID-19 severity. Along with this, studies on epigenetic factors regulating the ACE2 expression should also consider the genetic variants of ACE2 which might be more significant than studying epigenetic regulation alone for SARS-CoV-2 progression.

3.2. Epigenetic modifications of immune response during COVID-19

As described earlier, SARS-CoV-2 evolved several mechanisms to evade immune sensing, primarily by inhibiting IFN-I induction or by keeping its production at bay leading to delayed or inefficient functions of ISGs. Similarly, we also have discussed how different myeloid cells including monocytes, macrophages, and mDCs, although accumulated in infected lungs and becomes activated in response to locally secreted pro-inflammatory cytokines and chemokines (Liao et al., 2020) but seem functionally impaired in the periphery (Arunachalam et al., 2020). Further evidence showed that this pathogen induced downregulation of ISGs and other monocyte or macrophage signature genes are not only due to the impairment in the signaling cascade, but also by epigenetic mechanisms including histone modification like methylation and acetylation. Different regulatory genes of immune response have their promoters and enhancers susceptible to the modulation by such epigenetic marks, which play fundamental roles in the differentiation and determining the function of immune cells. Yang et al. (2022) investigated altered gene expression and histone methylation pattern in peripheral blood mononuclear cells (PBMCs) of COVID-19 patients. Although the study could find any difference in genome-wide histone methylation status of H3K4me3 and H3K27me3 between healthy subjects and COVID-19 patients, but identified significant differences in histone marks intensity near the transcription start site of several immune function related genes. Brauns et al. (2022) reported that acutely ill and severely affected COVID-19 patients shows significant functional impairment of circulating monocytes whereas severe COVID-19 convalescent subjects or patients of early recovery phase display modulation of monocyte function with distinctive transcriptomic and cytokine expression profile. The author identified variable chromatin accessibility at various gene loci of monocytes in acute and convalescent versus control COVID-19 patients by ATAC-seq. Gene ontology analysis further revealed strong enrichment for activating protein (AP1) and musculoaponeurotic fibrosarcoma (MAF) recognition element containing motif in the more accessible region in convalescent patients. The author also speculated that functional reprogramming of circulating monocytes driven by these epigenetic changes could contribute to the lingering complication of post-COVID 19 syndrome for a prolonged period. In another recent study by Maher et al. (2022) published on preprint server *bioRxiv* researchers investigated how SARS-CoV-2 infection lead to functional alteration of classical CD14+ monocytes towards a state of unresponsiveness characterized by defect in pro-inflammatory cytokine expression, NF-κB-driven cytokine responses and defective type I IFN response. The study showed that mild COVID-19 monocytes carry increased H3K27Ac and H3K4Me3 marks compared to controls, but moderate monocytes display comparable expression to healthy controls. There was no difference in the expression of H3K9Me2; H3K27Me3 expression was increased in mild monocytes compared to controls, not seen in moderate COVID-19 monocytes. These suggested the defective epigenetic remodeling and subsequent activation of innate immune functions in patients with moderate COVID-19. In the case of ISGs, it has been shown that upon stimulation, IFN-I and IFN-III induce histone remodeling complex which further induces the removal of repressive histone mark (H3K27me3) and recruitment of activating mark like H3K4me3 leading to the formation of open or active chromatin. This change in chromatin organization allows the transcription factors like members of STAT (signal transducer and activator of transcription) and IRF (interferon regulation factors) family proteins which drive the ISG expression. Both SARS-CoV and MERS-CoV have been shown to favor a closed chromatin conformation that inhibits ISG expression. STAT signaling was further shown to influence the expression of histone markers. Ishii et al. (2009) described that following IL-4 stimulation STAT6 binds at the promoter of Jmjd3 (jumonji domain containing protein D3), a H3K27 demethylase and induces its expression. The author also described that increased Jmjd3 contributes to the decrease of H3K27 dimethylation and trimethylation (H3K27me2/3) marks as well as the transcriptional activation of genes specific for M2 macrophages, a type tolerogenic macrophages (Ishii et al., 2009). Although not enough data is available on the generation and the role of M2

macrophages during SARS-CoV-2 infection, it can be predicted that an increase in the frequency of this subtype of macrophages could provide the virus a survival advantage. Along with histone modification, virus induced DNA methylation also plays a crucial role in the inhibition of ISG expression. As discussed earlier, a study by Menachery et al. (2018) revealed that MERS-CoV induces a global increase in DNA methylation, specifically at the MHC locus, and thus hinder the antigen presentation gene expression. Consistent with previous data, a recent genome-wide DNA methylation profile analysis of peripheral blood mononuclear cells isolated from critically ill severe COVID-19 patients also revealed hypermethylation of IFN-related genes and hypomethylation of inflammatory genes (Corley et al., 2021). This study also showed a significant association between a higher percentage of neutrophils with the perturbation of DNA methylation pattern in severe COVID-19 patients. In addition to ISGs, IFN-induced transcription-factor binding, chromatin remodeling, and changes in histone marks also occur at regulatory elements of other immune regulatory genes (genes whose transcription is not altered by IFN stimulation alone), including canonical targets of NF-κB that encode several pro-inflammatory cytokines. Several studies reported the crucial role of various histone deacetylases, mostly HDAC2 in governing the expression of these cytokines in monocytes and macrophages following activation. The nuclear localization of HDAC2 makes it convenient to inhibit the NF-κB activity, thus altering the monocyte and macrophage function (Weiss et al., 2020). However, the roles of HDACs have now been proven to be dichotomous. On the contrary to the commonly known role of HDACs as silencers of gene expression, several reports also showed HDACs to be closely associated with activating the transcription of ISGs in a non-canonical deacetylation independent manner. Therefore, chances are there that SARS-CoV-2 infection may affect HDAC activity to overcome the inflammatory responses. Indeed, a SARS-CoV-2 protein interactome study revealed that Nsp5, a major non-structural protein of the virus interacts with HDAC2 and may inhibit its transport into the nucleus, thus could potentially affect the ability of HDAC2 to mediate the inflammation and interferon response (Gordon et al., 2020). This study also identified a significant interaction between transmembrane E of SARS-CoV-2 and BRD2/4, members of the bromodomain and extra-terminal (BET) domain family of epigenetic readers that bind to acetylated histones to regulate gene transcription. The C-terminal region of SARS-CoV-2 'E' protein mimics the N-terminal segment of histone H3, which is also known as the interacting partner of bromodomains. Thus by mimicking the histone structure, the 'E' protein potentially disrupts the BRD-histone interaction, modulating the protein expression beneficial to the virus. Notably, histone mimicry is an evolutionarily conserved mechanism utilized by other RNA viruses like influenza and SARS-CoV also. Marazzi et al. (2012) showed that the carboxy-terminus of influenza A H3N2 protein NS1 and tail of histone H3 shares a homologous sequence. Targeted CRISPRi screening has identified BRD2 as a potential regulator of ACE2 expression in Calu-3 cells (Samelson et al., 2022), thereby controlling viral entry into the host cell. The study showed BRD2 knockdown significantly reduces the transcription of ACE2 as well as the Spike protein binding to the cells. Thus SARS-CoV-2 exploits various host epigenetic players, to trespass the immunosurvelliance primarily via modulating the expression of NF-κB target genes and ISGs (Marazzi et al., 2012).

Besides, ISGs and pro-inflammatory cytokines, TLRs are also crucial players of the innate immune response. Although signaling though different TLRs also converge with the induction of IFN-I/III and ISG response, nevertheless epigenetic signatures at the promoter of TLR genes have its distinct significance. TLRs are found to be enriched with H3K4me3 at their promoter. Epigenetic regulation and expression of TLR7 and TLR3 are specifically important for detecting ssRNA viruses and the dsRNA intermediates (formed during replication of these viruses) respectively. Like ACE2, TLR7 is also located on the X chromosome that gives a genetic advantage to the female immune system, as escaping XCI provides altered expression levels of it. This might be correlated with the lethality in males with loss-of-function variants of TLR7 after being infected by SARS-CoV-2 as compared with age and sex-matched COVID-19 patients without TLR7 mutations (van der Made et al., 2020).

3.3. Histone citrullination and COVID-19

In addition to modulating the anti-viral immune response, SARS-CoV-2 infection also inflicts NETosis mediated excessive tissue damage. Although the mechanism of NET induction is debatable, in severe COVID-19 patients, researchers have found elevated levels of cell-free citrullinated histone H3 (Cit-H3), a marker of NETs. Cit-H3 is positively correlated with increased cytokine IL-8, platelet, leukocyte, and granulocyte counts in COVID-19 (Leppkes et al., 2020). Cit-H3 is a product formed by deimination of arginine residues on histones, catalyzed by a family of protein arginine deiminase (PADs or PADIs) enzymes which on the other hand, becomes activated as a downstream molecule of neutrophil activation and calcium influx (Fig. 2). The family comprises of five highly conserved proteins PAD1–4 and PAD6, among which PAD4 is of particular interest in terms of epigenetic regulation. Citrullination of histone arginine residues promotes chromatin decondensation which further implicates increased transcription of genes. Notably, Veras et al. (2020) showed that blood neutrophils from COVID-19 patients release lesser quantity of NETs when incubated with Cl-Amidine, an inhibitor of PAD4, indicating SARS-CoV-2-induced release of NETs is PAD4-dependent. However, it is not yet clear if PAD4 activation is directly mediated by SARS-CoV-2 infection of neutrophils or by the pro-inflammatory cytokines and chemokines which are also known to enhance the recruitment and activity of neutrophils for NETosis during COVID-19 (Cicco et al., 2020). Altogether, these data suggest that histone citrullination, originated either by direct infection in neutrophils or via the 'cytokine storm' induced activation of neutrophils, plays a significant role in inducing NETosis during SARS-CoV-2 infection, thus increasing the vulnerability of individuals for developing a more severe form of COVID-19.

3.4. Link between epigenetic modifications associated with other comorbidities and COVID-19

Several theories have emerged explaining different factors playing crucial roles in affecting different populations of patients disproportionately during COVID-19, comorbidities being one of them. Feng et al. (2020) described that the percentage of comorbidities, especially diabetes and hypertension, are higher in severe and critical cases. Studies have reported significant various epigenetic factors associated with the onset and clinical manifestations of these diseases also contributed to promoting severity and the generation of several severe clinical symptoms during SARS-CoV-2 infection.

Several authors have mentioned how obesity and type 2 diabetes increase the propensity towards vulnerability in COVID-19 patients. Senapati et al. (2020) reported that the overexpression of dipeptidyl peptidase 4 (DPP4) through epigenetic modification at rs13015258-C allele is critical and could be related to the higher fatality rate among SARS-CoV-2 patients suffering also from Type 2 diabetes. Sartore et al. (2020) has suggested that DNA methylation of several genes regulating islet beta-cell function, as well as in insulin resistance of peripheral tissues such as liver, muscle, and adipose tissue are also known to play a crucial role in determining the severity of COVID-19 in subjects affected with diabetes.

We already have discussed the role of histone citrullination in promoting vulnerability to COVID-19 fatality. Histone citrullination has also been reported to play important roles in a lot of other human diseases such as cancers, autoimmune diseases, and thrombosis which are critical risk factors for severe COVID-19 disease also. Bioinformatics analysis revealed a strong interaction between SARS-CoV-2 S protein and the tumor suppressor protein, p53 (Singh and Bharara Singh, 2020).

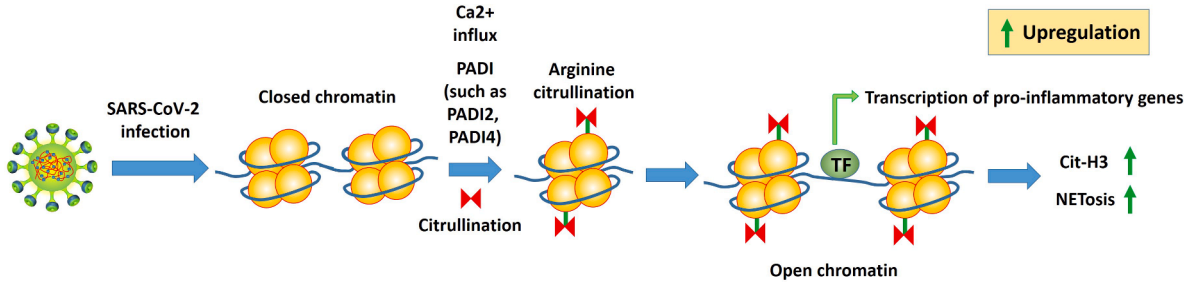

Fig. 2. Citrullination and NETosis during SARS-CoV-2 infection COVID-19 patients have shown a marked upregulation of histone citrullination on immune response genes, a type of epigenetic modification catalyzed by PADI. COVID-19 patients show upregulation of citrullinated histone H3, which is a marker of NETs. Histone citrullination decondenses chromatin which disrupts harmonious transcription of several genes, and as citrullination is upregulated in COVID-19 patients, it is important to study if and how that affects pathophysiology in COVID-19 patients. [Cit-H3: Citrullinated histone 3; PADI: Peptidyl arginine deiminase; TF: transcription factor].

Earlier, it has been reported that p53 via transactivating PAD4 regulates citrullination of histone chaperone nucleophosmin (Tanikawa et al., 2009) and also interacts with cit-H3 (Beato and Sharma, 2020; Li et al., 2010). Therefore, it is important to investigate how citrullination via epigenetic dysregulation can impact the pathophysiology in COVID-19 patients who are vulnerable due to comorbidities like cancers, autoimmune diseases, and thrombosis.

Cancer is a well-known risk factor associated with increased vulnerability to COVID-19 and various genes have been found to influence the comorbidities in COVID-19. Li et al. (2020b) suggested that overexpression of two cysteine protease enzymes, cathepsin L/B (CTSL/B), via DNA hypomethylation has been detected in pancreatic adenocarcinoma (panAD). On the other hand, these two proteases are particularly important for SARS-CoV-2 pathogenesis as they cleave the viral Spike protein into the S1 and S2 subunits, further mediating the fusion of the virus and host cell membrane. Therefore, higher expression of CTSL/B in panAD patients results in greater susceptibility to COVID-19. Another type of cancer, which also has been predicted to increase the vulnerability in COVID-19 is prostate cancer (PCa). Indeed, a population-based study revealed that PCa patients on androgen deprivation therapy (ADT) had a significantly lower risk of SARS-CoV-2 infection compared with patients not undergoing ADT or patients with any other types of cancer (Montopoli et al., 2020). Androgen receptors (AR) have also been reported to be involved in the pathogenesis of SARS-CoV-2 since activation of these receptors is believed to cause upregulation of TMPRSS2; a transmembrane protease facilitating the entry of SARS-CoV-2 into the host cell. Therefore, upregulation of ARs via epigenetic mechanisms in PCa patients can be speculated to predispose them to increased susceptibility to SARS-CoV-2 infection (Bahmad and Abou-Kheir, 2020). We already have seen that higher ACE2 expression enhances the risk of severity in COVID-19 patients with other comorbidities. ACE2 expression has been found to be higher in lung adenocarcinoma. Therefore, hypomethylation or histone acetylation mediated upregulation of these genes in various cancers can be suggested to substantially enhance the chance of severity in SARS-CoV-2 infection.

Understanding the expression pattern of several crucial genes having overlapping roles in other diseases as well as COVID-19 will help to determine the degree of severity in patients with comorbidities. An epigenome-wide association study and gene ontology analysis by Esteller and colleagues has identified differentially methylated CpG islands in 20 coding genes between asymptomatic/paucisymptomatic and severe COVID-19 patients. One among them is *pm20D1*(peptidase M20 domain-containing 1), a metabolic disease associated gene, implying its additional link as a potential modulator of the severity of SARS-CoV-2 infection (Castro de Moura et al., 2021). Although its role in COVID-19 pathogenesis has not been validated. Therefore, more research is required to identify and investigate the role of more such candidate genes, lying at the crossroads of many cellular and pathological pathways that further help to gain more insights into the variation of clinical manifestation of SARS-CoV-2 infection in patients with other comorbidities.

3.5. MicroRNAs and COVID-19

Micro-RNAs (miRNAs) have been identified as a major player in regulating various cellular and physiological responses. miRNAs are small ncRNAs of approximately 20–22 nucleotides. They can regulate gene expression post-transcriptionally either by blocking the translation of mRNA or altering its stability. Although not abundant, some *in vitro* and *in silico* studies have predicted that RNA viruses, like SARS-CoV-2, can mediate changes in the expression of cellular miRNAs leading to downstream changes in the host transcriptome that can be advantageous to the virus. However, changes in miRNA expression can also lead to the inhibition of viral genome replication and translation, thereby increases antiviral effector activities.

Host miRNAs involved in the regulation of ACE2 and TMPRSS2 receptor has an important significance in controlling the SARS-CoV-2 entry and replication and hence can be therapeutically targeted. Nersisyan et al. (2020) showed that JARID1B, an H3K4 histone demethylase can indirectly increase ACE2 expression by epigenetically suppressing the transcription of miR-125a-5p. Thus dysregulated expression of ACE2 protein as described in COVID-19 patients can be predicted to result from the loss of this epigenetic regulation, through change in the miR-125a-5p expression levels. *In silico* approaches have identified miR-200c-3p as an important regulator of ACE2 expression in multiple tissues and Lu et al. (2020) experimentally validated its expression in human embryonic kidney cells (HEK-293T) through luciferase reporter assays. The author also showed that in human induced pluripotent stem cell-derived cardiomyocytes, induced overexpression of miR-200c-3p resulted in lower levels of ACE2 expression. Two independent studies have predicted miR-1246 downregulates ACE2 by directly binding to its 3′UTR sequence. Increased expression of miR-1246 miRNA has been linked with ARDS while low levels of it has been found in the small airway epithelium of smokers in comparison to non-smokers, indicating a possible role for this miRNA in the respiratory tract pathologies (Khan et al., 2020; Li et al., 2020a). Besides ACE2, SARS-CoV-2 also uses TMPRSS2, to enter into the host cells due to which miRNAs controlling the expression of TMPRSS2 plays an important to determine the risk of the infection. Several miRNAs like miR-30a, miR-30c, miR-127, miR-194–3p, miR-200c, miR-361, and miR-423, let-7a-5p and let-7d-5p were identified as negatively correlated with TMPRSS2 expression. Although, most of these studies predicted that SARS-CoV-2 pathogenesis may alter the level of expression of these miRNAs, however, their expression has not been experimentally validated and detailed mechanistic data is still missing. More studies are required to unravel the molecular details of miRNA interaction with SARS-CoV-2.

Studies have also identified several host miRNAs which target the

SARS-CoV-2 genome. Balmeh et al. (2020) has shown a high potential interaction of miR-1307–3p to the 3′UTR of the SARS-CoV-2 genome. This miRNA can also target human gene expression responsible for cell survival and proliferation (BCL2, PI3K/Akt pathway), cellular transport (AP2, PIP5K), associated with virus cell entry and spread. Several miRNAs like miR-1202, miR-138–5p, miR-196a-5p, miR-506–3p, miR-4758–5p, and miR-506–3p have been predicted to target the SARS-CoV-2 ORF1a/b polyprotein gene, a crucial viral component responsible for viral protein synthesis and maturation and inhibit its cleavage. Although the target is remaining unknown, two independent studies have identified miR16–2–3p to be present in higher levels in samples infected with SARS-CoV-2 (Li et al., 2020b; Chow and Salmena, 2020). Another study by Fulzele et al. (2020)has further predicted that miR-16–2–3p targets all the SARS-CoV-2 genome but not the SARS-CoV, implying a potential and distinguished role for miR-16–2–3p in SARS-CoV-2 infection. miRNAs are also crucial epigenetic modulators of host antiviral immune response. Wyler et al. (2021) showed a significant increase in the expression of miR-155 in the human cell lines (Caco2, Calu3, and H1299) infected with SARS-CoV-2. Interestingly, coincident with this finding, the author also observed a 2-fold increase in the expression of the ISGs and tissue damaging cytokines, such as CXCL10 or IL6 in SARS-CoV-2 infected Calu3 as compared to SARS-CoV. Significantly, the authors also showed a reduction of pulmonary damage by elimination of miR-155, denoting that this miRNA could be considered as a potential therapeutic target for the treatment of SARS-CoV-2 infection. Khan et al. (2020) has reported dysregulation of several miRNAs triggered by SARS-CoV-2 infection and predicted their association with crucial immune signaling pathways like suppression of TLRs, TRAF6, and IFN-signaling pathways, etc.

Viruses also have been predicted to produce miRNA-like sequences or viral miRNAs that can dysregulate the host gene expression by targeting them and enable the virus to survive and proliferate unhindered in the host cell (Barbu et al., 2020). Saini et al. (2020) identified two SARS-CoV-2 specific miRNAs, namely MD3–3p and MD241–3p which target *p53* and *BMPR2,* respectively.

3.6. Aging and epigenetics: a liaison governing the predisposition and severity of COVID-19 in older individuals

One of the biggest riddles of COVID-19 is why older people are affected by it so disproportionately and what roles do the various epigenetic factors play to influence the outcome of the infection in them. Although several comorbidities which increase the chance of fatality in this disease, themselves get accumulated with age. However, they alone are incapable to explain why age is an independent risk factor. The theory of 'epigenetic aging' describes that as a concomitant part of responding to intra-and extra-cellular stimuli host cells accumulate several epigenetic changes throughout their lifespan which further serves as a potential underlying cause behind various manifestations of aging and simultaneous loss of resilience. Such age associated epigenetic changes have been implicated as major causes behind the severe outcomes in older COVID-19 patients.

We have briefly mentioned earlier how age associated changes in the expression of ACE2 in older individuals profoundly impact the clinical symptoms of COVID-19 differently in them as compared to young adults. Corley and Ndhlovu (2020) showed age-related reduction of methylation at one of seven CpGs in the ACE2 promoter and these CpG sites are bordered by long-range promoter-enhancer regions that may change over time. Although the reduction in methylation or hypomethylation of ACE2 indicates a higher level of its expression in older individuals, the age-wise variation of the expression profile of ACE2 is not yet clear. However, as ACE2 is the primary gateway of the virus into the host cells, epigenetic dysregulation of ACE2 can be predicted to impact increased viral loads and severe respiratory illness in older people.

In aged individuals, if ACE2 is responsible to ignite the damage by ushering SARS-CoV-2 into the host, the ailing immune system adds fuel to the fire by the aberrant triggering of all effector components. Aging brings two major changes in our immune system: an intrinsic functional decline of immune competence called 'immunosenescence' and secondly, chronic low-grade or subclinical systemic inflammation called 'inflammaging', both of which jointly contribute to the dysregulated immune response in older subjects (Fig. 3). Indeed, substantial evidence now indicates that T cell immunosenescence could be a major underlying cause behind the frail adaptive immune response whereas inflammaging for the cytokine storm in aged COVID-19 subjects (Domingues et al., 2020). Studies have found that lifetime accumulation of epigenetic changes in various genes of the immune cells has prominent roles behind these age-associated hallmark changes of the immune system. Therefore, the dysregulation of the epigenetic markers on the immune system related genes and the consequent changes in their expression during aging also can be speculated as major drivers that play crucial roles in predisposing older patients towards COVID-19 severity. T cells are the most profoundly affected immune cells by the aging process. Tserel et al. (2015) reported age-related hypermethylated CpG sites of silent genes and enrichment of repressive histone marks in CD8+ T cells from older individuals. The author also observed a strong correlation between methylation changes and gene expression of IFN-γ, CCL5, CCL7, CD27, and other T cell function genes. It is well known that epigenetic markers play fundamental roles in building T cell memory, thereby helping to generate long-lasting immunity after infection or vaccination. As part of the process of immunosenescence, alteration to these epigenetic markers or their complete losses contributes to the progressive lowering of lymphocyte renewal capacity through reduced hematopoiesis (Morrison et al., 1996) and involution as well as deterioration of thymus (Wang et al., 2021). Overall, this results in the loss of naïve and central memory cells and an expansion of short-lived effector memory cells, mostly within the CD8+ T cell compartment. As naïve T cell generation almost comes to a stop and clonal diversity of the existing T cell population decreases, the capacity to mount strong adaptive response goes down which is also important for humoral immunity- the induction of robust antibody response, an essential component for vaccine efficacy. This can be related to the reduced long-term vaccine efficacy and the possibility of SARS-CoV-2 reinfection in vaccinated older subjects. In addition, senescence induced reduction of lymphoid cell numbers and a proportionate increase of myeloid-derived cells such as monocytes/macrophages also increases the chance of inflammation in older individuals. While immunosenescence partially paralyzes the immune system by affecting T cells, inflammaging, on the other hand, significantly harms the body by causing elevated secretion of pro-inflammatory cytokines like IL-6 and TNF-α (Domingues et al., 2020). One of the significant reasons behind inflammaging in old subjects is the cell-free DNA whose level has been found to increase during aging as a result of an increased level of reactive oxygen species (ROS) and consequent DNA damage, tissue necrosis, defective clearance of apoptotic cells, and inflammation itself (Nardini et al., 2018). The loss of repressive epigenetic markers like methylation on both histone (like H3K9me3) and DNA and more in general, age-associated heterochromatin loss has been correlated to the inflammaging process. Thus far, it is evident that alongside ACE2, the accumulating epigenetic modifications in immune cells throughout the chronological age of an older individual lead to the immunosenescence, manifested by the lack of adequate degree of effector mechanisms essential for fighting viral pathogens and the inflammaging, exacerbated inflammatory response, which can accelerate and intensify lung tissue damage. Alongside the chronological age, SARS-CoV-2 infection also has been shown to alter epigenetic aging. Cao et al. (2022) estimated epigenetic age by genome-wide DNA methylation based epigenetic clock and telomere attrition in the blood samples of healthy individuals and COVID-19 patients. The author reported accelerated epigenetic aging and telomere length shortening in severe COVID-19 patients and there is a strong association between accelerated epigenetic aging with the risk of developing severe COVID-19. Moreover, the study also speculated that

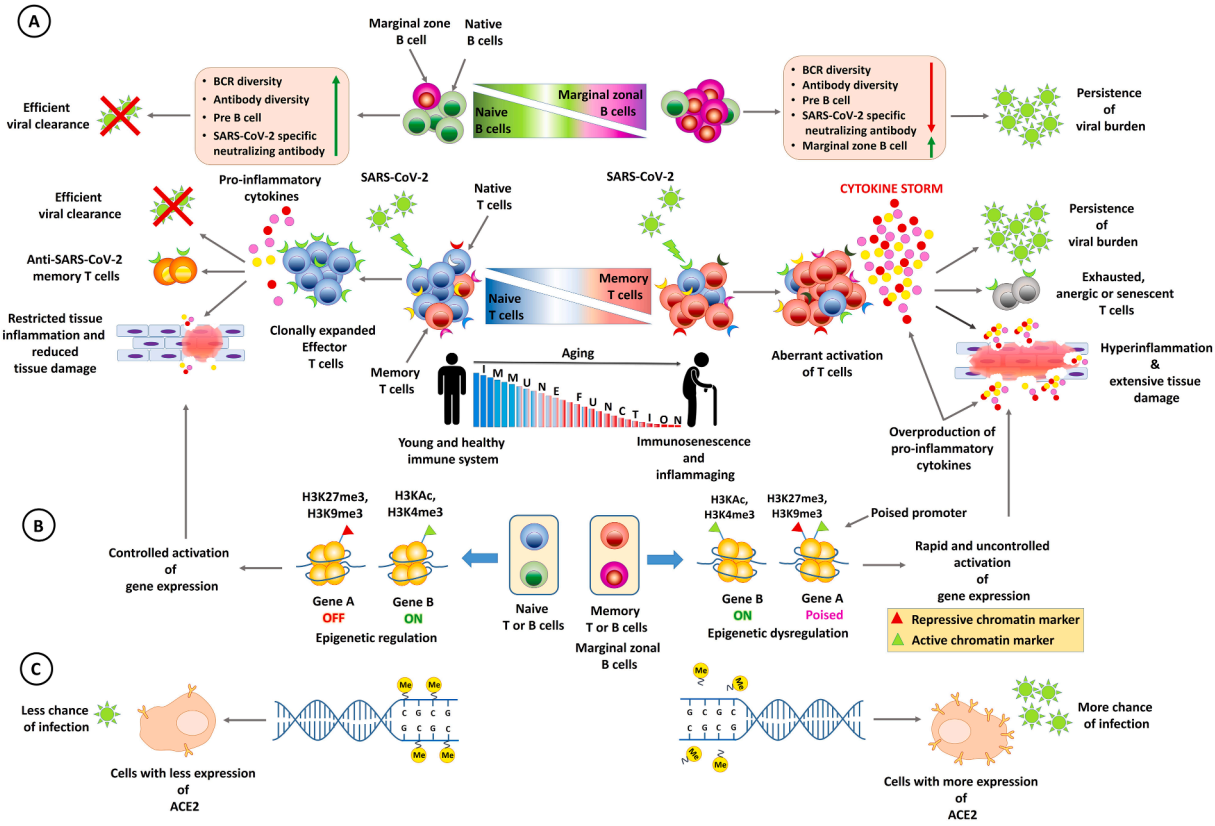

Fig. 3. Age associated epigenetic dysregulations increase the risk of COVID-19 fatality Various age associated epigenetic changes increase the risk of severe clinical symptoms of SARS-CoV-2 infection. Tightly controlled activation of both the innate and adaptive immune system as in young and healthy individuals is essential to thwart viral infection and clear viral burden, failure of which results in aberrant cytokine signaling, extensive tissue damage as well as the persistence of infection. (A) The lack of efficiency of the immune system to mount robust antiviral immunity in older individuals is primarily associated with gradual reduction of functional competence of the immune system, termed as "immunosenescence" and a consistent low-grade chronic inflammation, termed as "inflammaging". These two processes jointly affect both the T and B cell compartment (B) In young and healthy subjects, naïve immune cells are higher in number than memory cells and expression of genes related to immune response in them is strictly governed by repressive and active chromatin marks as well as DNA methylation while aberrant regulation of these marks or their losses results in discordant expression. Moreover, older individuals exhibit a higher proportion of memory T/B cells which are highly enriched with poised promoters, comprising of both transcription-activating histone marks like H3K4me3 and repressive marks like CpG methylation, H3K27me3, and H3K9me2. This results in rapid and uncontrolled activation of immune cells which further facilitate cytokine storm and other hyperinflammatory disorders. (C) Another factor that also contributes to increase vulnerability to severe COVID-19 in older subjects is the DNA hypomethylation mediated induction of higher expression of ACE2 receptor which further increases the chance of newer infection. [ACE2: Angiotensin converting enzyme 2; BCR: B cell receptor; H3K: Histone 3 lysine; Ac: Acetyl; Me: Methyl].

the accumulation of epigenetic aging and accelerated telomere attrition following SARS-CoV-2 infection might contribute to the development of post-COVID-19 syndrome. However, more studies are required to explore the association between age related epigenetic changes and the severity of COVID-19 which might further assist in the quest for treatments and the development of more potential vaccines for the elderly subjects.

4. Targeting epigenetic dysregulation in COVID-19: therapeutic strategies

A growing understanding of the association of various epigenetic mechanisms with COVID-19 pathogenesis can be utilized to develop potential therapeutic strategies that are capable of selectively targeting a diversity of 'writer', 'reader', and 'eraser' proteins involved in the regulation of those mechanisms. Small-molecule agonists or antagonist drugs targeting these epigenetic processes, henceforth called 'epidrugs' are already being used in cancer therapies, either alone or in combination with other immunotherapies, thus indicating an enormous potential of them for specifically modifying gene expression patterns. Although, not enough direct evidence about the effects of these drugs on the host response towards SARS-CoV-2 infection is presently available, repurposing of such drugs can be expected to substantially reduce viral burden as well as hyperinflammation and bring immune homeostasis. Based on these data, new molecules with better selectivity and efficacy can be synthesized. Moreover, epidrugs can also be rationalized to boost the COVID-19 vaccine efficacy by inducing memory T cells, thus enabling long-term immune protection. Besides small-molecule epidrugs, few immunomodulators like Bacille Calmette-Guérin (BCG) have also been strongly implicated in the treatment of COVID-19 via epigenetic remodeling of gene repertoires associated with immune regulation. Here, we will discuss the therapeutic potential of targeting dysregulated epigenetic mechanisms during COVID-19 by various available small-molecule epidrugs and immunomodulators.

4.1. HDAC activator

HDACs are important epigenetic regulators playing significant roles in viral transcription, replication, and maturation processes as well as regulation of inflammatory immune response. Sirtuins (SIRT1–7) are a major class of HDACs that are a major regulator of cellular energy stress and pathogen defense. For example, SIRT1, as discussed earlier is an important regulator of host entry of the virus via augmenting ACE2 expression and was found to be upregulated in the lung of patients with

severe COVID-19 comorbidities (Clarke et al., 2014). However, SIRT1 has anti-inflammatory roles also and was found to be downregulated in PBMCs of severe COVID-19 subjects which is coincident with the elevated plasma level of pro-inflammatory cytokines in them (Bordoni et al., 2021). Resveratrol, a potential activator of SIRT1 has been reported to promote anti-inflammatory effect by inhibiting NF-κB activity (Ma et al., 2015), thus implying its role in countering hyperinflammation in COVID-19. Moreover, resveratrol also has anti-viral effects. Yang et al. (2021) showed that post-infection administration of resveratrol inhibits SARS-CoV-2 entry and replication in cultured Vero cells. Earlier also, Lin et al. (2017) showed resveratrol administration significantly reduced apoptosis induced by MERS-CoV, prolonged cellular survival post-MERS-CoV infection, and also decreased viral titer. Various other sirtuin activators are summarized in Table 1 that can be beneficial as an adjunct therapy for COVID-19 by reducing hyperinflammation.

4.2. HDAC inhibitor (HDACI)

HDACs have been shown to interact with various viral nonstructural

Table 1
Therapeutic targets and potential role of currently available epidrugs in COVID-19.

Epigenetic modification	Inhibitor	Target specificity	Biological impact	Potential outcome in COVID-19
HDAC activation	Resveratrol (Ma et al., 2015)	Natural activator of Sirtuins. Mainly activates SIRT1, but also effects on SIRT3 and SIRT5.	(i) Improves overall cellular stress response,(ii) Inhibits NF-κB dependent pro-inflammatory activity.	(i) Reduces hyperinflammation(ii) antiviral effects (prevents viral entry and replication) (Rossi et al., 2021)
	SRT2104 (Mercken et al., 2014) SRT1720 (Minor et al., 2011)	Highly selective synthetic SIRT1 activator	Reduces pro-inflammatory cytokine secretion.	(i) Reduces hyperinflammation(ii) Target SARS-CoV-2 M^{pro} (Pitsillou et al., 2020)
HDAC inhibition	Vorinostat (SAHA) (Nehme et al., 2019)	Pan-HDAC	Diminished production of pro-inflammatory cytokines in response to LPS	(i) Reduces hyperinflammation
	TSA (El Baba and Herbein, 2020; Herbein and Wendling, 2010)		Reduces pro-inflammatory cytokine secretion, although cytotoxicity is a concern.	(i) Reduces hyperinflammation
	VPA (Shweta and Krishna, 2020; Zhang and Kuchroo, 2019)		(i) Affects inflammatory functions(ii) Reduced stimulation of Th1 response	(i) Prevents viral entry via downregulating ACE2 expression(ii) Reduces hyperinflammation
	Panobinostat (Takahashi et al., 2021)		(i) Affects several signaling pathways including MAPK, PI3K-Akt, and NF-κB crucial for cellular growth, metabolism and differentiation	(i) Restricts viral entry via suppressing ACE2 expression(ii) Reduce the risk of thromboembolism in severe patients by downregulating ABO gene transcription
HAT inhibition	Anacardic acid (Dekker et al., 2014)	p300 and p300/CBP associated factor (PCAF) inhibitor	Inhibits the NF-κB pathway	Can suppress cytokine storm.
	MG149 (Ghizzoni et al., 2012; Legartová et al., 2013)	Tip60 and MOF selective inhibitor	Inhibits expression related to the NF-κB and p53 pathways.	
	C646 (Bowers et al., 2010; Santer et al., 2011)	Highly potent selective inhibitor of p300	Increases apoptosis by inhibition of the androgen receptor and NF-κB pathway	
HKMT inhibition	DZNep (Zhou et al., 2019; Cole et al., 2016)	Mainly inhibits G9a but also regulates other HKMT like Ezh2	Regulates fundamental immune cell functions like differentiation, growth, plasticity and cytokine profile	(i) Reduce viral titer,(ii) Restore innate immune defense.
	BIX-01,294 (Kubicek et al., 2007; Loh et al., 2014)	G9a		Promote anti-viral state
	GSK126 (Arbuckle et al., 2017)	Ezh2		Restore ISG response
DNMT inhibition	5-azadC (El Baba and Herbein, 2020; Roulois et al., 2015)	DNMT1	(i) Hypomethylation of gene promoters(ii) Defective methylation and acceptor function of transfer RNA	(i) Restore ISG response(ii) Reduce hyperinflammation(iii) Viral molecular mimicry
	Azacitidine (Christman, 2002)		Hypomethylation of gene promoters	
BET inhibition	ABBV-744, CPI-0610, OTX015, JQ1, Apabetalone (Qiao et al., 2021; Gilham et al., 2021; Mills et al., 2021; Gibbons et al., 2019; Zhang and Kuchroo, 2019)	BRD2/3/4 (some has higher selectivity to specific BRD proteins)	Prevent pro-inflammatory pathways by inhibiting STAT3 activation, signaling through JAK-STAT pathway, RELA phosphorylation dependent cytokine production etc.	(i) Reduces hyperinflammation(ii) Prevent viral entry via downregulating ACE2 expression(iii) Reduce viral titer
Vitamins and natural products	Vitamin D Quercetin Epigallocatechin-3-gallate Curcumin (Andika et al., 2020)	Multiple epigenetic factors	Regulate fundamental immune cell function and inhibit aberrant activation of several pro-inflammatory pathways like inflammasome activation, NF-κB pathway etc.	(i) Reduces hyperinflammation(ii) Restore immune homeostasis

proteins. For example, Nsp14, a 3′−5′ exonuclease, crucial for coronavirus RNA synthesis interacts with SIRT5 (Minskaia et al., 2006; Budayeva et al., 2016). Nsp4, an important player in viral membrane fusion and replication has been shown to interact with HDAC2. Moreover, 3C-like protease (3CLpro), a component of SARS-CoV-2 protein maturation also binds to HDAC2 and prevents its nuclear translocation (Gordon et al., 2020). This implies that pan-HDACI, such as vorinostat or suberanilohydroxamic acid (SAHA), valproic acid (VPA) and trichostatin A (TSA), combined with antivirals, can be useful therapeutic agents to interfere with these processes. These drugs also have potential anti-inflammatory effects which can be helpful in countering the hyperinflammation in severe COVID-19. Singh and Bharara Singh (2020) reported that VPA downregulated ACE2 in endothelial cells and inhibited the expression of IL-6 and ICAM-1 (intercellular adhesion molecule 1) (Shweta and Krishna, 2020). Saiz et al. (2021) investigated the effect of VPA in diverse cell lines (HK-2, Huh-7, HUVEC, Caco-2, and BEAS-2B) on the expression of the ACE-2 and neuropilin-1 (NRP-1) receptors and found that VPA treatment significantly reduced the expression of these receptors in all of these cell lines. Moreover, the study also showed that treatment with VPA post-infection reduces viral replication as well as the production of inflammatory cytokines (IL-6 and TNF-α) effectively. Takahashi et al. (2021) investigated the effect of various HDACIs including sodium butyrate, sodium valproate, TSA, SAHA on the expression of ACE2 in two gastric carcinoma cell lines, KATOIII and NUGC-4, and found that in comparison to others, panobinostat caused the most drastic suppression of ACE2. Additionally, the group also reported that both panobinostat and sodium butyrate caused significant downregulation of ABO gene transcripts. Although the mechanism is not clear, an increasing number of reports have suggested an association between the ABO system and COVID-19 severity. Another potential HDACIs are SCFAs, such as butyrate and propionate which are naturally produced from fermentation of fiber-rich diets by commensal bacteria inhabiting in our gut mucosa (Rishi et al., 2020; Vignesh et al., 2021). Zhang et al. (2019) showed butyrate induced metabolic shift in macrophages towards anti-inflammatory M2 phenotype via the inhibition of HDAC3. Therefore, dietary supplementation with SCFAs either directly or via probiotic approaches can be tested as adjunctive therapy for reducing hyperinflammation in COVID-19. Ripamonti et al. (2022) investigated several effects two pan-HDAC inhibitors (givinostat and vorinostat) and a selective HDAC6 inhibitor, ITF3756 on immune and epithelial cells *in vitro*. The study found that both pan and HDAC6 selective inhibitors, have an anti-inflammatory effect on primary epithelial cells of the upper and lower respiratory tracts. Moreover, the study also showed that ITF3756 downregulates monocyte activation in presence of R848 (TLR7/8 agonist), dampens TNF-α mediated pro-inflammatory signaling cascade in monocyte, modulates adaptive immune response by decreasing T cell exhaustion and enhancing T cell differentiation towards a central memory phenotype. Given the aggressive inflammatory response and the large production of pro-inflammatory cytokines occurring during severe SARS-CoV-2 infections, all these effects could be beneficial for the treatment of COVID-19 patients. However, most of these studies have been performed using cell lines of different origins (tumoral, non-tumoral, and primary cells), the susceptibility and tolerance to diverse doses of these inhibitors could vary *in vivo*. Therefore, further studies in preclinical models followed by clinical trials in large cohort of patients to determine minimal effective dose and the therapeutic range depending on which they could be considered as potential antiviral drugs are required. In addition, it is also important to investigate the interaction of these HDACIs with major host proteins involved in the SARS-CoV-2 pathogenesis, specifically in preventing cellular entry of the virus. In conclusion, it can be suggested that HDACIs have immense potential as therapeutic epidrugs for the treatment of COVID-19.

4.3. Histone acetyltransferase inhibitor (HATI)

Histone acetyltransferases like p300 and CBP (CREB-binding proteins) have crucial roles in the activation of the NF-κB pathway and IFN-I response (Dekker et al., 2014). HATIs such as anacardic acid, MG149, and C646 have been reported to suppress IL-6 expression and NF-κB signaling thus can be predicted to dampen hyperinflammation (Dekker et al., 2014; Hu et al., 2017). Studies revealed that Nsp13, the SARS-CoV-2 helicase interacts with p300 but the detailed molecular mechanism is not known (El Baba and Herbein, 2020).

4.4. Histone lysinemethyltransferase inhibitor (HKMTI)

Various histone lysinemethyltransferase like G9a (catalyzes H3K9me2), SUV39H1 (suppressor of variegation 3–9 homolog 1, catalyzes H3K9me3), Ezh2 (enhancer of zeste homolog 2, catalyzes H3K27me3) regulates fundamental immune cell functions like differentiation, growth, plasticity and cytokine profile, etc. (Scheer and Zaph, 2017). Therefore, HKMTIs can be predicted to effectively restore dysregulated immune balance as hyperinflammation in COVID-19. Moreover, some HMTI like GSK126 (Ezh2 inhibitor), DZNep (G9a inhibitor) have potential anti-viral activity also (Daelemans et al., 1997; Arbuckle et al., 2017; Nehme et al., 2019). Ezh2 forms PRC2 (polycomb repressive complex 2) complexes which regulate ISG response. Pharmacologic inhibitors of PRC2 are currently undergoing clinical trials for cancer treatment and could be repurposed for the treatment of COVID-19. (Ayaz and Crea, 2020).

4.5. DNA methyltransferase inhibitor (DNMTI)

Decitabine or 5-aza-2-deoxycytidine (5-azadC), a nucleoside-based DNMTI, is widely known to inhibit DNA methylation in macrophages; thus, downregulating inflammation and IFN response and can be suggested for the mitigating cytokine storm (El Baba and Herbein, 2020; Patnaik and Anupriya, 2019). Notably, decitabine has recently been studied in a clinical trial for COVID-19 pneumonia-ARDS treatment (CTI: NCT04482621) (NCT04482621, 2020).

4.6. Bromodomain and extra-terminal protein inhibitor (BETI)

BETIs, such as JQ-1 and dBET6, also known as promising anticancer drugs may function by impairing the interaction of BRD4 with viral transmembrane ‘E’ proteins (Gordon et al., 2020). In recent years, several other BETIs with a superior binding affinity towards either bromodomain (BD1 or BD2) of BET proteins like ABBV-774, apabetalone (previously called RVX-208), OTX015 have been developed. Qiao et al. (2021) reported that JQ-1 and OTX015 decrease SARS-CoV-2 infectivity and ACE2 levels in H1437 lung adenocarcinoma cells. Gilham et al. (2021) demonstrated that apabetalone, a BD2 selective BETI downregulates the expression of ACE2 in Calu3 (human lung epithelial cells) and Vero E6 (monkey kidney epithelial cell) and consequently, attenuates SARS-CoV-2 ‘S’ protein attachment with the host cell surface and abrogates infection when treated with live SARS-CoV-2. In addition, the authors also showed that in Calu3, apabetalone significantly downregulates the cell-surface abundance of DPP4, a potential cofactor for SARS-CoV-2 entry into host cells, thus blocking the SARS-CoV-2 entry further. Mills et al. (2021) described that INCB054329 prevents cytokine storm-induced diastolic dysfunction in human pluripotent stem cell (hPSC) derived cardiac organoids, downregulates SARS-CoV-2 infection induced key inflammatory response genes in hearts of K18-human ACE2 transgenic mice, reduces endogenous ACE2 expression, and potentially blocks SARS-CoV-2 infection in 2D cultured hPSC-cardiac cells. The author also described that a 3-day pre-treatment of apabetalone also reduced ACE2 expression and viral infection. Resverlogix has recently announced a phase 2 clinical trial with apabetalone to investigate its effect on COVID-19 severity (Ray et al., 2020).

Samelson et al. (2022) reported pharmacological inhibition of BRD2 by JQ1 and ABBV-744 led to significant downregulation ACE2 expression in Calu-3 cells, induced pluripotent stem cell (iPSC)-derived cardiomyocytes, primary human lung epithelial cells and reconstructed human nasal epithelia, thereby thwarting SARS-CoV-2 infection. The author further showed that ABBV-744 remarkably decreases viral RNA count in golden Syrian hamsters. BETI can also affect host immune responses. For example, JQ-1 reversibly suppresses IFN-γ production (Gibbons et al., 2019), thus could be used to potentially attenuate the cytokine storm associated with COVID-19. Collectively, these findings suggest that BETIs may be of therapeutic benefit to prevent or reduce the impact of SARS-CoV-2 infection.

4.7. Vitamins and natural products

Vitamins like vitamin D (Vit.D) and some naturally obtained bioactive compounds like polyphenols (resveratrol, curcumin), flavonoids (quercetin, hesperetin) along with their derivatives (epigallocatechin-3-gallate or EGCG) are potential epigenetic modifiers and have significant capacity to repair dysregulated immune response. Vit.D has been described to induce immune tolerance and exogenous administration of Vit.D has been shown to delay the progression of several autoimmune diseases or ameliorates the disease severity (Colotta et al., 2017; Koivisto et al., 2020). This indicates its possible role in suppressing COVID-19 cytokine storm. Numerous clinical studies investigating the association of Vit.D deficiency with the progression of COVID-19 severity and the prophylactic effects of Vit.D supplementation on COVID-19 outcome have been registered in last year (Euctr2020-001602–34-Fr, 2020; Hospital, 2020; NCT04385940, 2020; NCT04482673, 2020). Curcumin regulates a plethora of epigenetic mechanisms like inhibition of DNMTs, demethylation of partially methylated CpG sites, reduction of p300/HAT activity, etc. which can be useful in suppressing the hyperinflammation associated with COVID-19 mortality. EGCG, present in high concentration in green tea can be another ideal candidate epidrugs for COVID-19 treatment owing to its potential role in epigenetically modifying key cellular signaling pathways related to inflammation, oxidative stress response, cell cycle, etc. (Haslberger et al., 2020; Andika et al., 2020).

4.8. Immunomodulators as epidrugs

Emerging studies revealed an inverse relationship between the global incidence of COVID-19 and BCG vaccination policies; countries where the BCG vaccination program is active show lower incidence and reduced mortality rate from COVID-19. BCG has been shown to provide non-specific heterologous immune protection against several unrelated diseases. Studies have found that BCG vaccination triggers 'trained immunity', a form of innate immune memory characterized by the reprogramming of metabolic and epigenetic networks of innate immune cells which 'train' those cells to prime a quicker and robust immune response upon stimulation with the same or other non-specific antigens. Several authors have suggested that prophylactic vaccination of BCG may prevent the incidence of COVID-19 in high-risk individuals. Basak et al. (2021) have described that along with triggering anti-viral response via trained immunity BCG also promotes tolerogenesis. The authors hypothesized that while trained immunity facilitates quicker reduction of viral burden via locally inducing robust secretion of pro-inflammatory cytokines and restoring IFN-I signaling, the induction of immune tolerance mainly via promotion of Treg proliferation helps to dampen cytokine storm. Therefore, via finely tuning our epigenetic machinery BCG can provide a spatiotemporal control from COVID-19. Geller and Yan (2020) reported the potential effects of β-glucan on restoring the immune dysregulation and suppressing the cytokine storm observed in COVID-19. In their studies, they observed that β-glucan--driven trained immunity governs some epigenetic changes and that could be used as a valuable target for COVID-19 treatment.

5. Epidrugs as potential therapeutic tool for boosting SARS-CoV-2 vaccine efficacy

All currently available COVID-19 vaccines have been developed with a primary focus on the generation of high-affinity neutralizing antibodies. Owing to the capacity of selectively modulating the gene expression, epidrugs hold a great promise in boosting the efficacy of COVID-19 vaccines. These pharmacological agents can be helpful in inducing durable responses to vaccination via keeping the promoters and/or enhancer of pro-inflammatory genes in monocytes/macrophages and NK cells in open conformation, thus facilitating enhanced responsiveness after restimulation with the same or a different non-specific stimulus (de Bree et al., 2018). Such epidrugs can render long-term innate and adaptive responses without the causing a strong acute inflammatory response. Epigenetic modifications of the hematopoietic progenitor cells in the bone marrow by such epidrugs can be highly beneficial as these cells convey their changes to the various immune cell populations, allowing the maintenance of elevated responses for prolonged period of time (Chavakis et al., 2019). The differentiation and long-term maintenance of memory T and B cells rely on a specific DNA methylation signature that correlates with activation-induced gene expression (Komori et al., 2015). Youngblood et al. (2011) showed that cells which develop into long-lived memory CD8+ T cells can show reversal of epigenetic repression of naïve cell-associated genes while effector genes remain unmethylated. In addition to the building of memory response, epidrugs can also be employed to reinvigorate exhausted T cells (T_{ex}), a population of T cells primarily characterized by high expression of inhibitory receptors like PD-1 (programmed cell death protein 1) and linked to severe viral infection as in SARS-CoV-2. T_{ex} cells exhibit distinctive transcriptomic and epigenetic profiles in contrast to effector and memory counterparts. Epigenetic modulation combined with therapeutic blocking of inhibitory receptors might be able to generate viral-antigen specific T cells, presumably with greater efficacy and more durability (Tough et al., 2020). Vaccination of elderly subjects and patients with other comorbidities is essential since they are vulnerable to greater risk of infections while being treated for other diseases, like cancer. However, due to the immunocompromised state of these patients, live vaccines may result in fatal consequences. In this scenario, the co-administration of potential epidrugs along with non-live vaccines could be useful to enhance the protective effects of these vaccines and take advantage of the epigenetic remodeling of the cells to protect against the disease.

Key questions

1 Can epigenetic mechanisms of ACE2 expressing cells be targeted to spatiotemporally control its expression in both young adults and elderly individuals to restrict viral entry into the host cells and subsequent induction of inflammatory immune cells?
2 Can epigenetic mechanisms be targeted for conversion of exhausted T cells into SARS-CoV-2 antigen specific memory T cells? However, strategies should involve checkpoints that prevent systemic effects on self-reactive exhausted T cells that may otherwise contribute to the onset of autoimmunity.
3 Can overtly active myeloid lineage cells that majorly contribute to the 'cytokine storm' be converted to exhausted phenotype?
4 Can epidrugs be used to boost vaccine efficacy by facilitating the generation of SARS-CoV-2 antigen specific memory T cells rather than short-lived effector T cells?
5 Can epidrugs be used to reprogram metabolism of innate and adaptive immune cells that in turn alter their functions against SARS-CoV-2 infections?
6 Can epigenetic approaches be used to induce tolerogenesis in both innate and adaptive compartments of immune system which can be beneficial to suppress acute or hyperinflammatory symptoms?

6. Future perspective and conclusion

The initial exponential surge of COVID-19 although has been now brought under control but some countries like India, Japan are still struggling with the subsequent wave of COVID-19 fatality. While mass vaccination is still the utmost priority to vanquish COVID-19, potential therapy capable of reducing the viral titer and reversing the dysregulated host responses are still required to curb the spread of infection and fatality. In the past months, the fast-evolving field of COVID-19 has garnered several crucial information regarding disease pathogenesis. Growing understanding of the role of epigenetic processes in governing host-pathogen interaction and their alteration during SARS-CoV-2 infection indicated that these mechanisms can be selectively targeted to either prevent them from being hijacked by the virus or to restore them in favor of the host. This review has summarized the recent findings on the various epigenetic aspects of SARS-CoV-2 infection and also suggests potential epigenetic therapies. However, the current knowledge about the interaction of SARS-CoV-2 proteins with host epigenetic machinery largely originates from bioinformatics analyses which need to be validated experimentally also. Therefore, more extensive research is still required to obtain greater resolution about the SARS-CoV-2 induced alteration of host epigenetic mechanisms and their intersecting nodes with other cellular functions like metabolism and immune response. This might help to build a more comprehensive map of epigenomic networks and identify SARS-CoV-2 specific key chromatin regulators controlling the transcription signatures of innate effector molecules during the hyperinflammatory responses. Systematic analysis of SARS-CoV-2 epigenome and viral genome-associated chromatin regulators in host cells during infection phases are required to understand the transition of infection and the mechanisms of symptomatic versus asymptomatic infection and inflammation. Moreover, unraveling more details about the association of epigenetic factors in COVID-19 will also help us to understand how targeting them can result to elicit SARS-CoV-2 specific T cell memory which may boost beneficial responses of the vaccine. It is also necessary to integrate all epigenetic mechanisms and to consider epigenetic factors as highly dynamic and interactive players with cellular metabolism by using multi-omics approaches. Remarkable progress in the understanding of the epigenetic mechanisms governing the cellular function coupled to the pioneering advancement of new drug discovery platforms leads to the development of small-molecule based epidrugs targeting regulatory proteins of those mechanisms. Although, currently no epidrugs have received formal approval for application in clinical setting, however, various such drugs which already have shown promising results in other diseases like cancer and cardiovascular diseases can be repurposed for use in COVID-19. As these epidrugs target the host, unlike the antivirals which mainly target the viral-encoded factors, therefore in comparison to monotherapy with conventional antivirals, it can be hypothesized that the epidrugs singly or combined with those antivirals may provide a promising strategy against the emerging mutant strains of coronavirus also.

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