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Data Associated with Epigenetic Changes Brought by SARS-Cov-2

Enlightment on the Treatment and Public Health Practices

Tianze Qiu
Admiral Farragut Academy Tianjin
Tianjin, 300000, China

***Abstract*-In this year, COVID-19 and Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) became a major public health issue. After countless researchers' efforts, many biological properties of SARS-Cov-2 and infection pathways have been deciphered. Nevertheless, there are currently many unresolved issues. For instance, the disparity between the severity of the symptoms brought by SARS-Cov-2 is one of these issues. Because it is believed that many biological pathways are the results of the interplay between genetic and epigenetic pathways, this article seeks to explain the these unsolved issues by analyzing the data associated with hosts' epigenetic regulation. Considering the importance of Angiotensin converting Enzyme 2 (ACE2) and the frequent presence of comorbidities in critically ill patients, the article hypothesizes that it is the comorbidities that bring the changes in host epigenome and cause a severe form of COVID-19. The purpose of this paper is to make a thorough inquiry about whether the comorbidities bring he changes in host epigenome and cause a severe form of COVID-19. After randomly searching and analyzing many data papers, many evidences are found to support this idea. Therefore, this paper hypothesizes that it is the comorbidities cause the changes in host epigenome and exacerbates the symptoms led by COVID-19. Based upon this hypothesis, there are many potential treatment options and implications to the public health system.**

Keywords-Data science; SARS-Cov-2; public health; epigenetics; ACE2

I. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 has posed a great threat to human health. In spite of the great accomplishments made by the globally collaborative efforts, many unfathomed problems still exist. For instance, the diversity in the severity of the symptoms caused by SARS-Cov-2 demonstrates a more in-depth understanding of the biological mechanisms of this novel Coronavirus is still urgently needed [1]. This diversity in symptoms definitely has numerous contributing factors. The role of epigenetic mechanisms is one that needs further explore and analyze. Angiotensin converting Enzyme 2 (ACE2) type I can be a great candidate for the study of epigenetic mechanisms in SARS-Cov-2. The reason lies in the fact that it plays a crucial role in the viral entry to the host cell and the expression of it is thought to be highly correlated with COVID-19. Besides, it has been found that the chief risk factors associated with a severe form of COVID-19 are certain comorbidities, including lupus, some cancers, and diabetes mellitus, as shown in Table 1 [17,18]. This finding gives a hint to study the correlation of ACE2 expression and these complications. Therefore, this article hypothesizes that the major changes in epigenetic regulations caused by these comorbidities are responsible to exacerbate COVID-19. In the following parts, this article seeks to find whether this hypothesis can be validated or not.

II. IMPORTANT ROLES OF ACE2 IN SARS-COV-2 INFECTION

After several special cases of pneumonia was found in Wuhan, China at the end of 2019, this novel type of pneumonia spread to other provinces in China in an outrageous way. Later, this new type of pneumonia was found to be highly related to a unique coronavirus, which was named as 2019nCoV by World Health Organization and later renamed as severe acute respiratory syndrome coronaviruse-2(SARS- CoV-2).

Previous studies have found many factors at the host cell which are related to viral entry. Angiotensin converting Enzyme 2 (ACE2) is the one that this article attaches great importance to discuss.

Heretofore, researchers performed extensive analysis of clinical specimens. Later, it was found ACE2 expressed in enterocytes of the small intestine, in alveolar cells of lung, and in smooth muscle cells of a wide range of organs seemed to be very active in clinical samples from patients with COVID-19 [2]. Apart from this evidence, another research which studied the infection of epithelial cells demonstrated that hardly can SARS- CoV-2 infect the undifferentiated epithelial cells expressing a low level of ACE2, as shown in Table 1 [3].

Generally speaking, ACE2 is a metalloenzyme containing a peptidase M2 domain and an amino acid transported domain that generally binds with SARS-CoV-2. Normally, it takes an important role in cleaving phenylalanine residue and producing vasodilator angiotensin. However, when the host cells make contact with SARS-CoV-2, ACE2 plays a significant role in viral binding. As a result, the reason underlies the fact that human can be effectively infected by SARS-CoV-2 is that there are two hot spots for viral binding in human ACE2. Moreover, frequent mutations at receptor-binding motifs can also be regarded as the chief culprit of human infection since these mutations typically occur near the two hot spots. For instance, N501T mutation which can boost the binding capacity of SARS-CoV-2 is one of this kind of mutations [4].

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TABLE I. THE EFFICIENCY OF VIRAL ENTRY LED BY SARS-COV-2 IN THREE TYPES OF CELLS [3]

Type of cells	β-galactosidase expression after transduction with unit: RLU ($\times 10^{-3}$)/ μg protein
A549	Around 0.5
Poorly differentiated submerged hTBE cells	Around 1
Highly differentiated hTBE cells (with highest ACE2 expression)	Around 3.5

Changes in the epigenetic regulations of ACE2 gene cause the exacerbation of COVID-19. Many of human bodies' biological properties are results of the coaction between epigenetic and genetic mechanisms. Human's immunity of this novel virus, SARS- CoV-2, is therefore not an exception. There are numerous scientific evidences to demonstrate the correctness of this idea.

For instance, by studying the epigenetic regulation of IFN-γ, an important interferon in antiviral activities, in patients with coronaviruses, it has been found that MERS-CoV utilizes DNA methylation to decrease host cells' potency of antigen presentation, as shown in Table 2 [5]. This discovery suggests the possibility that SARS- CoV-2, a coronavirus sharing many similarities with MERS-CoV, also maneuvers host' immune system and therefore increases the possibility for the virus to spread by changing the host's epigenome.

TABLE II. THE DOWN-REGULATED IFN-Γ RELATED GENES IN DIVERSIFIED CATEGORIES [5]

Classifications	H5N1, %	H1N1, %	MERS, %
Complement	57.1	0	54.1
Cytokine	11.1	11.1	33.3
MHC	86.7	6.6	80
ISG	18.2	0	18.2
Receptors	66.7	33.3	50
Ubiquitin	60	0	40
Binding proteins	37.5	0	37.5

Sample size: n = 15 genes
Responsive genes are divided into down-regulated in case that log2 FC < 0
MHC: Major Histocompatibility Complex, an important antigen-presentation molecule

As mentioned earlier, this article seeks to figure out whether the comorbidities associated with SARS- CoV-2 lead to the changes in host epigenome. Considering the significance of ACE2 mentioned above, this article chooses lung tissue to study, because there are many genes locating in the human lung that regulate ACE2. These genes include the ones that directly relate to some important epigenetic enzymes that enable the successful viral entry.

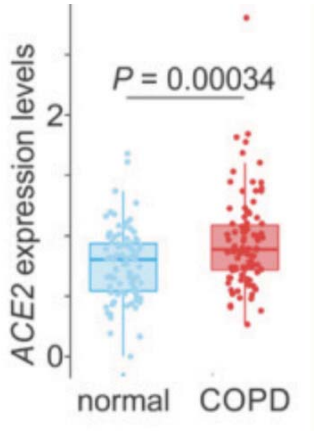

Figure 1. The investigation of ACE2 expression in human lungs with Chronic obstructive pulmonary disease [6]

The difference between the patients with COPD and controlled individuals t-test p-value is 0.00034

In a study, researchers found out that some hosts' epigenome was altered when they were studying the lung tissues of the patients with SARS-CoV-2 and the comorbidity, the type 2 diabetes [6]. These alterations encompass an obvious increment of the regulation of a histone deacetylase, SIRT1, and histone modifications of H3K27Ac, H3K4me1, H3K4me^3 in ACE2 genes, all of which affect human genome by increasing ACE2 expression.

Moreover, a previous study can also readily indicate the sexual difference in terms of the severity of symptoms led by SARS-CoV-2 [7]. From preceding epidemiological studies, males are more prone to be infected by SARS-CoV-2 than females, as shown in Table 3 [8,17]. From a cohort study showing the correlation between gender and health outcome, the fact males are more likely to become smokers is shown, as shown in Table 4 [9]. As a result, it is possible to attribute this sex disparity to smoking. It can also be inferred that smoking may use a similar mechanism, changing the epigenetic regulation of ACE2 gene, as what has done by some comorbidities in human lung, considering smoking's well-known impact on altering human genomes by DNA methylation [10]. In that study, a meta-analysis of DNA methylation was conducted. By using the Illumina BeadChip

450K, researchers assessed the DNA methylation on participants in 16 cohort studies which included 2433 current smokers and 6956 people who never smoked before. By comparing these two groups, it turned out that 2636 CpGs, 1405 genes, were differentially methylated in a significant manner under Bonferrni threshold (P-value < 1×10^{-7}).

TABLE III. SEXUAL DISPARITIES IN COVID-19

Sample	Percentage of male patients	Reference
58 Chinese patients	67%	[17]
1099 Chinese patients in 552 hospitals within 30 provinces	58%	[8]

TABLE IV. SEX DISPARITIES IN SMOKING PATTERNS IN USA [9]

Health outcomes	Men	Women
Smoking in the past month	42%	34%

In order to have a comprehensive understanding of the impact brought by the comorbidities on hosts' epigenome, only focusing on patients' lung tissues is not a compelling idea. Fortunately, a study utilizes co-expression analysis of ACE2 provides the big picture [11]. By conducting Pearson correlation to find genes related to ACE2 and adopting FDR correction to prove the significance of the data, the team successfully find several genes which seem can affect the expression of ACE2. These genes included 544 genes with positive relation and 173 genes with negative correlations. One of these genes, lysine demethylase 5B (KDM5B) demands great attention. In an earlier research, patients with breast carcinoma experiences an increment of KDM5B histone demethylase and the boost of the expression of ACE2 [6]. KDM5B is a great candidate to explain the boost. Known to all, the chromatin accessibility is highly related to KDM5B. To be specific, during transcription, KDM5B is one that can lead the deportation of di-methylation and tri-methylation, two basic chromatin markers, from the lysine 4 of histone H3.

As breast carcinoma has been proven to be a comorbidity altering host epigenome with the presence of SARS- CoV-2, whether other cancers can have the same effect becomes an intriguing question. In a study, besides breast carcinoma, endometrial carcinoma and kidney renal papillary cell carcinoma are also confirmed to be highly correlated with an increased ACE2 expression [12]. This discovery was found by using TIMER in TCGA database (*P-value <0.05, **P-value <0.01, ***P-value <0.001). The reason probably underlies in the fact that these two diseases are able to decrease the DNA methylation of ACE2 promoter, leading increased ACE2 expression and causing a change in hosts' epigenome. This finding can further support the hypothesis that comorbidities can alter the epigenetic regulation of ACE2 in hosts, and thus improve the chance for SARS- CoV-2 to spread.

III. POTENTIAL TREARMENT OPTIONS

The fierce spread of SARS-CoV-2 forced countless scientists to spare no efforts in developing novel treatments, but most of the current treatments inevitably had some downsides. First, there was some ingenious treatments focusing on hindering the viral entry. For example, scientist used the existing neutralizing antibodies targeting on the receptor binding domain (RBD) of SARS-CoV. However, it is reported that although SARS-CoV and SARS-CoV share great homology, about 75.5%, many epitopes in the novel virus was different from SARS-CoV, revealing an urgent need to develop new antibodies, as shown in Table 5 [13]. Apart from this category of treatments, some researchers attach great important on disrupting the replication of SARS-CoV. Remdesivir is the most compelling antiviral drug in this division, but there is not sufficient data to validate its efficacy. In addition, because patients with a severe form of symptoms always suffered cytokine storm, some scientists conceived up using corticosteroids which can suppress dysfunctional inflammation to make them get rid of this life-threatening danger. Nevertheless, NHC guidelines totally deprecates the using corticosteroids in a systematic manner, implying the risk of this treatment. Even though there are more than 15 candidates for the vaccine, for the sake of safety, they are currently all undergoing clinical trials and none of them have been on the market yet.

TABLE V. ALTERATION OF ANTIGENICITY OF SARS-COV-2 [13]

Classification of epitopes	Percentage of novel epitopes
All kinds	85.3%
Antibodies in the RBD regions	85.7%
High-score antibody epitopes in SARS-CoV-2	90.9%

Taking the flaws of the current treatment into consideration, it is urgent to develop some novel ones. The article tries to present some new treatments targeting on epigenetic mechanism. The Extra-Terminal Domain (BET), the epigenetic

readers which can identify chromatin with acetylation, has been proved to play a crucial role in latent viral life [14]. Scientists could test whether the treatments with BET inhibitors are effective in this virus, SARS-CoV. Last but not least, it has been found numerous compounds in nature, such as methyltransferase inhibitor curcumin and sulforaphane can elicit the epigenetic silencing of ACE2 genes [15]. On the grounds that epigenetic regulations of ACE2 genes are important in viral entry, scientists should find more of these compounds.

IV. IMPLICATIONS TO PUBLIC HEALTH MANAGEMENT

Considering the high rates of spread, COVID-19 can definitely be seen as a huge threat to the public health system. Luckily, countries all over the world have spared no efforts in curbing the spread of the virus and all of them have made accomplishments. However, the deficiency of medical supplies, such as ventilators, made some critically ill patients could not receive proper treatment. This predicament was probably caused by the fact that some patients with mild symptoms used too many resources. The reason why the government could not have a sagacious use of the supplies was that they could not predict which patients would confront life-threatening symptoms.

In this circumstance, this article will give some great advice. The current public health surveillance system, the data collection system, remains immature. For instance, United States of America currently only collected basic data, such as hospitalizations, death, visits to emergency departments via the existing influenza surveillance systems and National Vital Statistics System. In contrast, as the close relationship between the severity of the symptoms and the presence of comorbidities was demonstrated previously, the government should also collect the comorbidities patients have through the surveillance systems. In this way, they could categorize which patients need intensive treatment, thereby wisely allocating the medical supplies.

V. CONCLUSION

Through the discussion in the paragraphs above, it has been proven that the reason why patients with both comorbidities and SARS-CoV-2 are more likely be infected and have a severe form of symptoms is that the hosts' epigenome are altered in this case and makes the hosts' immune system more susceptible to the virus than usual. On the basis of this hypothesis, the article proposes some novel the treatment options which focus on the epigenetic regulation of ACE2 genes. Many implications to the public health policies are also mentioned, including the one that incorporates patients' comorbidities into the surveillance system. Although this hypothesis is validated to a certain degree, more clinical data are urgently needed to support this hypothesis. In addition, there are still some unsolved questions require further investigation. For instance, when the viruses attach the S proteins on cells' surfaces, protease TMPRSS2 plays an important role. Thus, whether the epigenetic regulations of the gene related to TMPRSS2 are significant in the viral life cycle becomes an intriguing question that needs further exploration.

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