Epigenetic modifications of Covid-19 – A probable mechanism for viral infection and transmission

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Abstract— The global pandemic Corona Virus Disease- 19 (Covid-19) has shaken world by its drastic spread and morality rate. The threat is still continuing without much control. The need for treatment strategies to improve survival rate is mandatory to save the human kind. Though the mode of virus spread from human to human transmission is identified, yet the spread cannot be controlled. Once the virus is entered in the human body, it is able to modify the immune system in such a way that the affected individual becomes very weak and susceptible for secondary infections involving multi organs and ultimately leading to death. There must be a mechanism by which the virus could modify the host environment for its multiplication. This review article is focused on the possible epigenetic changes, which modify the morphology of Covid-19 virus in to a much aggressive one to target multi organs of the host leading complete immune suppression. However, these are only the possibilities of how the virus survives in different conditions to adapt and attack new hosts for rapid transmission of the disease. Plenty of studies on epigenetic changes of the viral genome are to be conducted in order to understand the mode of integration of the virus in the host cell as well as to derive proper medications to control the transmission.

Keywords— Covid-19; epigenetic changes; viral integration; transmission

INTRODUCTION

The current pandemic of Covid 19 has evoked the world to think about the accelerated need of diagnostic strategies, development of vaccines and other therapeutics to treat and control the disease as early as possible. This dreaded pandemic was emerged suddenly in Wuhan, China in December 2019 and was spread to the rest of the world by March 2020. Corona virus disease or Covid is an infectious disease caused by corona virus whose mode of transmission is mainly through the droplets of the affected person while sneeze, cough or even exhales [1]. That is the reason why social distancing is advised as a protective measure in addition to use of personal protective equipments (PPE). Corona virus is similar to Severe Acute Respiratory Syndrome (SARS)-Cov and Middle East Respiratory Syndrome (MERS)-Cov and is of animal origin [2]. The major target tissue in humans is the epithelium of respiratory tract, which then multiply and spread through viral integration and slowly affecting other system too. It is still unknown how and when the disease is spread and why there is an increase in rate of spread. One possibility is the constant morphological changes of the virus to adapt the different conditions worldwide. This review is focused on the probable adaptive changes of Covid-19 through epigenetics which ultimately alter the immune system of the affected individual susceptible for multiple infections. However more studies are required to conduct the mode of transmission and the integration of the virus in humans for discovering the correct therapeutic measures.

Morphology of Covid-19

Covid 19 virus is an RNA containing retro virus. Known as Sars Cov-19, Sars Cov-2, novel corona virus (nCoV) or 2019 n-COV. Electron microscopic images have revealed that these viruses are spherical in shape and are covered with an envelope. The recently reported SARS-CoV-2 viruses are also spherical in shape like other corona viruses with spikes of proteins projecting from their surfaces. These spikes help in attaching to the host cells. The genetic material of the virus is RNA and that single stranded RNA is found to be attached with the nucleoproteins. This RNA-nucleoprotein combination is embedded in a capsid with matrix proteins [3]. The spikes of proteins on the envelop has array of glycoproteins. Some of these viruses may contain a hem agglutinin-esterase protein also [4]. The single stranded positive sense RNA (Mr6X106) is able to integrate with the host cell genome [5]. The glycoproteins are able to attach to the host cell and they carry the antigenic epitopes which can be recognized by neutralizing the antibodies [6]

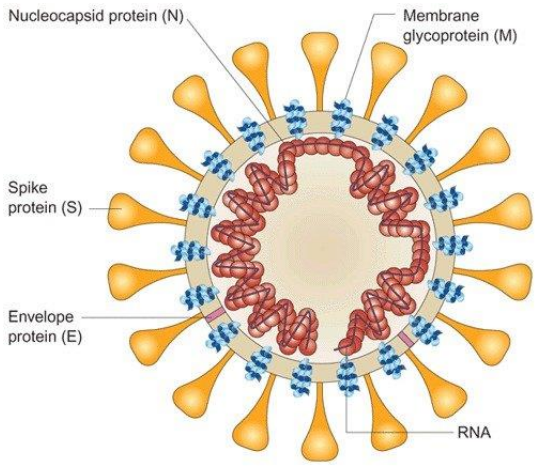

Fig 1: Structure of Covid-19

Mode of Transmission

The virus that causes COVID-19 is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. These droplets are too heavy to hang in the air, and quickly fall on floors or surfaces [1]. As per the studies and evidences corona viruses are extremely fast in transmission and grow only in differentiated respiratory epithelial cells. The infected cells may change their morphology by converting into vacuolated with damaged cilia and may form syncytia. Once the cell damage occurs, inflammatory mediators are generated increasing the nasal secretion, local inflammation and swelling. This in turn leads to sneezing, obstruction of the airway, and raised temperature of the mucosa and body [7]. The transmission may be quick through wet surfaces and through contacts. There is currently no data available on stability of 2019-nCoV on surfaces. Data from laboratory studies on SARS-CoV and MERS-CoV have shown that stability in the environment depends on several factors including relative temperature, humidity, and surface type. WHO continues to monitor existing evidence around novel corona virus (nCoV) and will update when such evidence is available.

Viral Integration

The assumption is that the coronavirus enter the cells mainly through specific receptors. A study concluded that, the receptor may contains aminopeptidase N and sialic acid residues as in the case of two strains of Covid ; 229E and OC43 classified as alpha and beta corona virus respectively [8]. Like other two viruses (COVID-19) uses a particular protease called TMPRSS2 to prime the spikes to attach with the receptor This receptor ligand binding is possible with the activation by this protease [9.10]. Once there is entry of the virus into the host cell, the viral coatings are shed off resulting easy integration of the viral genome into the host cell genome resulting transcription as well as translation. The same study revealed that the replication results in the formation of nested set of mRNAs with common 3' ends and specific region on 5' ends may get translated! Of the seven mRNA produced, the shortest one codes for nucleoprotein and remaining direct the synthesis of further segments of the genome. These proteins are then assembled at the cell membrane and the formed genomic RNA is then joins.

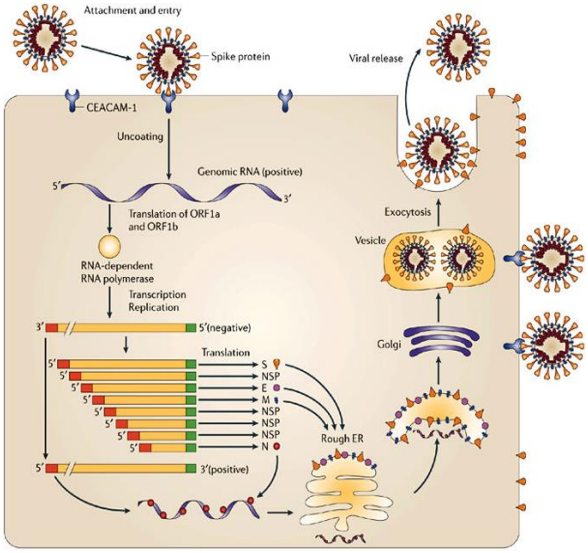

Fig 2: Viral integration of Covid-19

There are other studies also in which, analysis of the structure have revealed that receptor angiotensin-converting enzyme 2 (ACE2) is a host receptor permitting the virus to enter the cell and infect [11]. Interestingly this ACE2 was also identified as a host receptor for other corona viruses including SARS-CoV and NL63 [12]. It is discovered that the SARS-CoV-2 spike of proteins was 10 to 20 times more likely to bind ACE2 on human cells than the spike from the SARS virus previously discovered. This may enable SARS-CoV-2 to spread more easily from person to person than the earlier viruses. Hence a more aggressive mechanism might have been operating in case of Covid-19. Studies have also shown that ACE2 protein and mRNA expression occurs in a variety of human tissues including lung, liver, stomach, ileum, colon, and kidney [13, 14]. Probably that explains the involvement of multi organs in SARS-CoV19 and severity of the disease.

Epigenetics

Epigenetics is the phenotypic change of the gene due to external and environmental factors. Epigenetic modifications occur during development and cell proliferation to regulate transcriptional activity in normal tissues [15]. Epigenetic modifications remain as cells divide and in some cases can be inherited through the generations. Environmental influences, such as a person's diet and exposure to pollutants, can also impact the epigenome. Histone modification and DNA methylation are the commonly occurring epigenetic changes in DNA [16]. However in RNA it is

by RNA modifications. These changes will ultimately mask the expression of the genes, hence the protein products may not be formed. Typically in a viral infection like in Covid19, when viral-host interactions takes place, DNA/RNA methylation, chromatin remodeling, and histone modifications may takes place which will regulate, remodel and change the gene expression pattern in the host. It is very important to note that the rapid spread of the pandemic is probably may the outcome of this epigenetic change to adapt the virus with the new hostile environment. Yet another possibility may be the forceful epigenetic changes are mandatory for the virus for its survival in different hostile conditions.

Epigenetic modifications of Covid 19 infection

The genomic and bioinformatics analysis has revealed that corona viruses possess the largest genomes of about 26.4–31.7 kb among other known RNA viruses. Variable numbers of small Open Reading Frames (ORFs) are seen between the various conserved genes downstream to the nucleocapsid gene in coronaviruses [17]. Since Covid19 is an RNA virus, its native structure and functions can be altered by RNA-modifications or epigenetic changes as per the adaptability commonly referred as epitranscriptome. This epigenetic changes and subsequent regulation has potential ability to maintain stable gene expression when necessary with the flexibility to respond to changes in environment [18], which may be a probable cause of the multiplication of Covid 19 virus. The transgenerational epigenetic regulation has got a pivotal role in the same. A recent study on SARS Cov -2 has revealed the epigenetic dysregulation of *ACE2* and interferon-regulated genes suggesting increased COVID-19 susceptibility and severity in lupus patients and explain why they are more susceptible for the infection [19]. Further in patients with other co-morbidities, the changes undergone by the virus may be drastic and rapid. The epigenetic changes can be important regulators that remodel host chromatin structure, gene expression patterns in a highly flexible manner. These changes can alter the cellular behavior including the host's innate immune response [20]. The changes in the internal environment of the host cells via these epigenetic changes make the virus to multiply in a much favorable condition created by it [21]. It is to be noted that the epigenetically modified virus can target the immune system of the host much easier than the unmodified virus in terms of its structural and functional efficiency.

Future insights and Conclusion

Though these information are based on the available DNA methylation studies and data of similar infections of past; extensive studies are needed to solve the epigenetic mechanism involved in this viral infection and its rapid mode of transmission from human to human by adapting the conditions in order to treat, manage and increase the survival rate. While developing vaccine also these modifications are to be taken into consideration.

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