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Covid-19: a novel challenge to human immune genetic machinery

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Introduction

COVID-19 also called as corona virus emerged in China in December 2019 and turned into a global pandemic in a short period of time (Corman et al., 2020). This viral infection manifested in humans as a respiratory infection with the signs and symptoms of fever, cough, generalized body aches, and fatigue. Some people presented with gastric upset like diarrhea and respiratory symptoms ranging from mild to severe that led to pneumonia and even death in severe cases (Wang, Horby, Hayden, & Gao, 2020).

Patient presentation

Usually, the Covid-19 patient presents with the signs and symptoms of respiratory illness. Cough commonly dry cough associated with myalgias and sometimes breathing difficulties due to decrease in oxygen saturation rates are present in these patients. Some people show fever with body aches while some are relatively asymptomatic (Wang, et al., 2020; Zhu et al., 2020). The severity of disease may sometimes worsen especially in the presence of associated co-morbidities and can lead to metabolic disturbances, chest tightening, and secondary complications. Some people show severe electrolyte disturbances and
might worsen leading to delirium, unconsciousness, and drowsiness. In extreme cases, coagulation disorders, multiorgan failure, and even death are present, leading to increased mortality. This increased need of ventilators and interventions like central line etc. in case of severely sick covid-19 patients.

Transmission: Corona virus is primarily transmitted in humans through respiratory route and is highly contagious (Peng et al., 2020). This transmission may also be by oral and buccal fluids, sprays and sneezing, direct contact, and also by means of airborne droplets. Therefore, the use of face masks may prove beneficial for the prevention of the spread. This is also aided by the use of sanitizers by maintaining hand hygiene.

Invasion into human body: After invading into the human body, the virus may lead to a sequence of processes such as viral invasion, replication, and programmed cell death i.e. apoptosis. Finally, the viral fragments disseminate that further leads to immune response generation and promotes inflammatory reactions inside the body. However, sometimes, inflammatory storms and eventually hypersensitivity reactions take place that lead to severe pathological damage in some cases. Occasionally, our body defense system may be fatal due to hypersensitivity reactions and subsequent anaphylaxis leading to pathological damage.

Receptor

After invasion into the cell, SARS-CoV-2 enters cells through the human angiotensin-converting enzyme 2 as receptor with the external surface unit of N-terminal (S1) of the spike (S) protein. This then uses the host trans-membrane serine protease 2 for S protein priming, thereby allowing fusion of viral and cellular membranes. Furthermore, the viral RNA genome enters mainly into the cytoplasm of lung alveolar epithelial cells, liver, heart, kidney, brain and intestine (Hoffmann et al., 2020; Liu et al., 2020b). The viral maturation produces multiple copies of virus, and escapes from the host cells to infect newer cells.

A target for noncoding micro-RNA is represented by the mRNA region of this protein in the viral genome. In this case, the viral spike mRNA translation will be blocked after hybridization with the selected complementary mi-RNAs. A synthetic mi-RNA can be used to inhibit viral genomic mRNA replication by reducing the expression of RNA-dependent RNA polymerase (Kang et al., 2020; Peng et al., 2020). When the body is infected with any viral infection, mi-RNAs plays essential role in immune response modulation. By targeting host cellular RNAs or viral RNAs during various infections mi-RNAs can lead to suppression of gene expression (Li, He, Wu, Yang, & Yi, 2020; Zhao et al., 2018). In Covid-19 patients, mi-RNA expression regulates immune response.

Structure of Corona virus

Corona viruses are made of single stranded RNA present within the coat proteins. The virus has a diameter of nearly 80–120 nm. Covid-19 virus
infection proved to be the utmost adversity to human health. Viral replication, transcription, and translation take place inside the host cell. When virus invades the host cell, it is able to use the host cell to survive and complete its living activities. Micro RNA is endogenous noncoding RNA but regulates many functioning processes inside body. These mature mi-RNAs molecules are formed from the primary transcripts by a series of cleavage processes with the help of various nucleases. These are then re-assembled into RNA induced silencing complex also known as RISC. Recognition of target mRNAs is done by complementary base pairing, and the translation of the target micro-RNA (Afonso-Grunz & Müller, 2015).

Fatality

Covid-19 has affected many individuals globally; and many have also died due to this disease which led to global health threat and a burden to health care systems worldwide.

Role of comorbid illnesses in Covid-19

It has been suggested by various studies that comorbid illnesses affect outcome in Covid-19 patients. Diabetes mellitus, cardiac problems, hypertension and other metabolic illnesses have adverse health outcome in these patients.

Treatment modalities

There were no effective therapeutic agents against this virus (Han, Lin, Jin, & You, 2020). However, some basic drug cocktails have been proposed for these patients. Prescriptions of antibiotics like cefixime, azithromycin and some antihelminthic drugs such as ivermectin have been given in Covid-19 patients. Use of multivitamins and vitamin c also proved helpful in maintaining the immunity in these patients. Conservative treatment and use of antipyretics was always appreciated in Covid-19 patients. However, with the advent of vaccines effective preventive measures have been developed. Vaccines have proved as a sign of hope in these crucial times when the health care system is overburdened due to this pandemic.

Emergence of vaccines

Vaccination is based mainly on viral genome interruption. They provide the immune response in controlled dose manner. When a person is given vaccine shot it reciprocates as immune reaction and subsequent antibodies formation within some span of time. Various vaccines have come up and have provided good efficacy against Covid-19 symptoms. To synthesize vaccines and design therapeutic targets molecular aspects of the disease needs to be focussed upon. In the example of Covid-19 treatment and therapeutic drug
development was enormously challenging. However, studying the viral molecular structure helped in resolving this problem and development of vaccines through continuous research on the viral molecular aspects.

**Molecular aspects of corona virus**

*Micro RNAs*: The micro-RNA is defined as single-stranded RNA molecules that are noncoding in nature. They have an estimated length of about 22 nucleotides and help in post transcriptional regulation of gene expression (Murmann et al., 2020). Micro-RNAs are believed to regulate many types of cancers (Liao, Li, Wang, Li, & Zou, 2018; Tang, Wan, Yang, Teschendorff, & Zou, 2018). Viral micro RNAs regulate the host cell expression and also viral target genes by inducing mRNA cleavage, breakdown, translation, inhibition etc. This leads to change in host cell activity and also viral replication process (Bernier & Sagan, 2018). Virus needs self protection and survival to invade the host immunity. Thus, identification of viral mi-RNA molecules and their genetic functions is very important. To develop the therapeutic measures in Covid-19 infection it is important to know the description of viral molecular structure and the micro RNAs as well (Wang et al., 2014; Zhao, Wang, Chen, Wan, & Wang, 2017).

Formation of viral proteins takes place inside the host cell; therefore knowledge of the exact functioning of mi-RNAs may help to fight against viral multiplication inside the host cell. Classically the mechanism of mi-RNA regulation towards their target gene is by binding to the 3’ untranslated region also called as 3’ UTR of the target mRNA. This may enable negative regulatory effects on gene expression. To do this, the selected mi-RNA must be able to particularly bind to the target mi-RNA of the viral genome or any other part of its genome (Ivashchenko, Rakhmetullina, & Aisina, 2020). This will help in development of miRNA-targeting antiviral therapy globally.

**Exosomes**

Almost all normal and pathological cells form exosomes and are found in all body fluids. These biological nano particles have an average diameter of between 30 and 100 nm in size. Exosomes are essential in this cell-cell communication process. Thousands of exosomes are released normally by cells every day. However, various pathological conditions lead to overproduction of these exosomes (Wang et al., 2018). Exosomes when released into the body fluids contain various microRNAs and some proteins that act as biomarkers. When such bioactive molecules are transferred from donor to target cells via exosomes this leads to reprogramming of the recipient cells (Grundhoff, 2011). Thus, the specific exosomes secreted by infected cells that contain the biomarkers may be used to predict the diseased condition (Venturella, Carpi, & Zocco, 2019). Micro RNAs encapsulated within
exosomes are amazingly stable in circulation because of the protection offered by exosomes against RNase-mediated degradation (Baldassarre et al., 2020).

In case for immune response generation, in autoimmune diseases and cancers micro RNAs has proved to play a pivotal role (Yoshimura & Kubo, 2007). This possibly suggests that microRNAs may be used as diagnostic biomarker for diagnostic utility and also as therapeutic targets in the disease treatment. Micro RNA-155 is a micro-RNA that is formed from the noncoding RNA transcript of the proto-oncogene B cell integration cluster (Elton, Selomon, Elton, & Parinandi, 2013).

**Immune cell development and importance of micro RNAs**

A high expression has been shown by micro RNAs especially miR-155 in case of both the inborn and acquired immune systems. Dendritic cells are devoted for initiation of adaptive immune responses. Micro RNA-155 controls DC-induced stimulation of CD8+ T cells by down regulating SHIP1 and also regulates DC-CD4 T cell interaction (Goncalves-Alves et al., 2019). Moreover, by targeting Jarid 2, miR-155 plays an essential role in mature DC migration to the T cell area of draining lymph nodes (Wang et al., 2016). Macrophages are also essential for the beginning of immune response in the early phases of infectivity. As per literature, miR-155 may also help in propagation of macrophages. Micro RNA 155 helps in secretion of pro-inflammatory cytokines such as interleukin 6 and Tumor necrosis factor alpha by targeting SHIP1 and SOCS1 respectively (Jiang et al., 2019). Additionally miR-155 that targets miR-155 down regulates macrophage polarization by suppressing the interferon gamma induced JAK2/STAT1 pathway and TLR/NF-κB signaling A (Yoshimura & Kubo, 2007; Zhang et al., 2016).

Abnormal host cells such as tumor cells or those infected with various pathogens are scavenged by natural killer cells (Yokoyama, Kim, & French, 2004). Research suggests that miR-155 upregulation led to increase in the number of natural killer cells therefore, improved the function of secreting interferon gamma. This enhanced antibody-dependent cytotoxicity by decreasing the expression of SHIP1 and increased the initiation of ERK and AKT kinases (Trotta et al., 2013). Some studies suggest that micro RNA 155 cause reduced expression of Noxa and SOCS1 in NK cells, thus increasing antiviral immunity in natural killer cells (Zawislak et al., 2013).

Antibody-secreting plasma cells are formed from B cells as well as control immune responses by cytokine secretion and antigen presentation (Lund & Randall, 2010). Micro RNA-155 is also crucial in the development of B cells by targeting SMAD 5 and also by modulation of the transforming growth factor (TGF)-β pathway (Jiang & Aguiar, 2014; Rai, Kim, McKeller, Dahia, & Aguiar, 2010). Micro RNA-155 affects B cell maturation steps by
controlling the production of cytokines and targeting different transcription factors M (Prinz et al., 2002).

Cytotoxic T lymphocytes or CD8+ T cells can recognize and kill virus-infected cells and tumor cells (Appay, Douek, & Price, 2008). Micro RNA-155 deficiency reduces the function of CD8+ T cell response with respect to various viral and bacterial infections (Gracias et al., 2013). It has been established that if miR-155 targets SOCS 1, antiviral response and signaling of cytokines in effector CD8+ T cells may be seen (Dudda et al., 2013). Therefore, miR-155 may serve to be essential in context to immune function of CD8+ T cells.

Other roles of micro RNA

Micro RNAs are believed to play an essential role in many regulatory pathways like progression, virus defense mechanisms, haematopoiesis, cell propagation, and programmed cell death. It has also been suggested that various mechanisms help viral mi-RNAs to encourage the breakdown of mRNAs and regulate the expression of host cells and viral target genes (Cheng et al., 2019; Harwig, Das, & Berkhout, 2014). Thus, viral micro RNAs may also prove helpful in formation of drugs for covid-19 and also many other diseases.

Immune response

For controlling Covid-19 and or even for resolution of the infection, immune response plays an essential role. However, if the immune response is exaggerated this may lead to self damage even at cellular level and may be associated with a hyper immune response. MicroRNAs are important for interaction between the host cell and the virus (Girardi, Lopez, & Pfeffer, 2018; Rupaimoole & Slack, 2017).

Hypersensitivity reactions

Although different drugs are given in case of Covid-19 infection, individual response is different in different individuals. In some individuals body own defense mechanism proved deleterious and has led to unwanted results and side effects. This might be attributed to cytokine storm.

Cytokine storm

A considerable number of hospitalized Covid-19 patients showed a systemic dysregulation of various pro-inflammatory cytokines called cytokine storm (Zhou et al., 2020). In these patients, such exaggerated inflammatory responses are associated with extensive lung damage and microangiopathy.
This also leads to endothelial and microvascular dysfunctioning, eventually leading to lung damage and secondary complications manifested as damage to various important organs (Varga et al., 2020). In case of hospitalized Covid-19 patients a good number of clinical trials are conducted to evaluate the efficacy of the anti-cytokines or antibodies against cytokine receptor as the part of treatment protocol. Drug named Tocilizumab is a monoclonal antibody against the interleukin-6 receptor (Crisafulli, Isgro, La Corte, Atzeni, & Trifiro, 2020; Liu et al., 2020; Luo et al., 2020; Xu et al., 2020).

Increased levels of Interleukin-6 were present in patients of Covid-19. The levels of miR-146a-5p were relatively reduced in comparison to healthy age-matched subjects. Therefore, imbalance between the physiological axis of IL-6/miR-146a-5p is present in the pathogenesis of SARS-CoV-2 infection. Comparable findings were reported in view of sepsis (Benz, Roy, Trautwein, Roderburg, & Leudde, 2016).

Micro-RNAs may be introduced directly into the blood or by inhalation into the lungs by incorporating micro RNAs into exosomes or vesicles. Introducing selected mi-RNAs into the blood will lead to suppression of the viral reproduction in the blood. Therefore, this may prove as therapeutic development in various diseases and also in case of Covid-19. In future proposed methods used for inhibiting the reproduction of corona viruses may also be used for other viruses.

**Cytokine release syndrome**

It is a common observation in patients with Covid-19. In this syndrome, there is activation of immune cells and large amount of cytokines are released into the circulation. This has varied effects on both the in borne and acquired immunity. Some of the studies suggest that inhibition of inflammatory cytokines should be avoided while treating patients with Covid-19 (Moore & June, 2020). Computational prediction of mi-RNAs in SARS-CoV-2 revealed target genes involved in pulmonary vasculature and antiviral innate immunity. In the genomic-age, there are now more ways for studying the biology of mi-RNA, the most common being the genome-wide identification of small noncoding RNAs (Lai, 2015). A number of researches suggest that several viruses encode microRNAs, which are able to down regulate the expression of genes directly. These genes are involved in various immunological reactions, apoptosis, axon guidance and also in cell differentiation pathways (Carl, Trgovcich, & Hannenhalli, 2013; Cullen, 2013).

Tumor suppressor p53 also called the molecular policeman has an important role in innate immunity. It decreases viral replication and infection and up regulates many genes of type I IFN transcriptional target (Rivas, Aaronson, & Munoz-Fontela, 2010). nCoV-MD241−3P target BMPR2 (bone morphogenetic protein receptor type 2) which is involved in TGF-β signaling pathway. Upon viral infection, BMPR2 gets suppressed and leads to
pulmonary vascular homeostasis (Andruska & Spiekerkoetter, 2018). Different viral miRNAs and their target gene silencing have been explained by many studies (Kim, Iizasa, Kanehiro, Fekadu, & Yoshiyama, 2017; Naqvi, Shango, Seal, Shukla, & Nares, 2018).

Conclusion

Corona virus is extremely infectious and spreads largely through the respiratory pathway in humans. The immunological response is critical for managing Covid-19 and, in some cases, even for resolving the infection. However, Corona virus seems to evade immune reaction by affecting immune system-regulating genes.

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