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SARS-COV-2 AND COVID-19: INFECTION AND BCG INDUCED IMMUNITY

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ABSTRACT

Background: Coronavirus disease 19 (COVID-19) which has its causative agent as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a disease that spread so quickly throughout the world, and has tormented the world ever since its discovery in November, 2019 in Wuhan, China. Due to the poor understanding of the infection pattern and pathogenesis, management and control of the disease has been difficult which has progressed to a global pandemic.

Materials and Methods: Information for writing the review paper were obtained from publications in various scientific journals and periodicals.

Result: The possible route of infection of susceptible cells and effect on human immune system have been discussed as well as the possible beneficial role of BCG vaccination in the protection of the population against COVID-19 and other viral infections.

Conclusion: Our knowledge of the virus for now is still very low. However, results and new data on COVID-19 will keep emerging daily. We should be mindful of the populations that are at risk of infection and basic researches aimed at increasing our understanding of the virus and the disease should be initiated so as to enable early development of a vaccine and development of a standard treatment protocol.

Keywords: SARS-CoV-2, infection, ACE2, immunity, lymphocytes, transmission, BCG

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1.0 Introduction

Coronaviruses are a group of viruses which are pleomorphic in nature, enveloped and measure 60-220 nm in diameter. The Coronavirus family derived their name from the spike (s) glycoproteins that are on the surface of the viruses which are crown-like in appearance. The spike (S) glycoproteins are club-shaped which measure about 12-25 nm in length (Saif and Jung, 2020). The genetic material found in Coronaviruses is a single stranded positive-sense RNA molecule that weighs between 26 and 32 kb (Saif et al., 2019). They consist of large number of variant forms and their rate of mutation and recombination is high (Forni et al., 2017, Domingo et al., 1998). Thus this encourages the development of new Coronavirus strains whose host specificity and cell tropisms are altered. These observed properties enhance their ability to be transmitted from one species to another including humans (Saif and Jung, 2020). Severe acute respiratory syndrome Coronavirus (SARS CoV-2) is thought to reside naturally in bats from where it was spread via civet cats that served as intermediate animal hosts to human beings (Li et al., 2005, de Wit et al., 2016).

Coronavirus disease 2019 which has been nicknamed COVID-19 is an infectious disease caused by the virus, SARS-CoV-2 which belongs to the *Coronaviridae* family and the genus *Betacoronavirus* (Saha *et al*., 2020). COVID-19 has caused several thousands of deaths all over the world after it was first isolated and characterized in the city of Wuhan, China towards the end of 2019 (Zhou *et al*., 2020, Zhu *et al*., 2019). Symptoms of this disease as observed in very seriously affected individuals could include the following; atypical pneumonia that manifests in the form of dry cough, prolonged fever, and severe shortness of breath and hypoxia, which may be followed by diarrhea and most times in severe case failure of several organs in the body, especially, the respiratory and cardiovascular systems (Guan et al., 2020, Vetter et al., 2020).

2.0 Materials and Methods

Information used in compiling this review were obtained from data in various publications of researchers who have conducted scientific studies about Coronavirus, response of human immunity to Coronavirus and BCG vaccination. These publications include scientific journals, and scientific periodicals from scientific organisations and regulatory agencies of government.

3.0 Result and Discussion

3.1 Method by which SARS-CoV-2 Infects hosts

SARS-CoV-2 makes use of spike glycoproteins on its surface to adhere and penetrate into epithelial cells as well as other types of cells through a surface receptor on the surface of the cells, called Angiotensin Converting Enzyme-2 (ACE2). The first step in the infection process is the binding of ACE2 by the virus with its spike glycoprotein, thereby deceiving the cell into engulfing it through endocytosis. From there the infection starts. By this binding of ACE2 the virus makes sure that the ACE2 is fully occupied and therefore will not be able to carry out its regular regulatory function(s); ACE2 is an important controller of the renin-angiotensin system,

that controls systemic fluid-salt-balance (Patel et al., 2017) and blood pressure. The expression of ACE2 enhances the widening of blood vessels; ACE2 converts hypertensive angiotensin II to angiotensin 1-7. This then decreases the pressure of blood flowing in the blood vessels (Hamming et al., 2007). ACE2 is also expressed in several organs in the body such as the lungs, heart, liver, brain, intestine, kidney, adipose tissues and testes (Kuba et al., 2010, Li et al., 2020, Gupte et al., 2008). The expression of ACE2 in these organs and tissues is of great importance to the body. There it carries out important local regulatory functions like enhancing mitochondrial function (Kuba et al., 2010, Ting-Ting et al., 2018); it is important for healthy functioning of the heart, protects the lungs from failing abruptly as a result of infection and improves beta-cells such that they function optimally and promotes insulin sensitivity (Turner et al., 2004, Crackower et al., 2002, Imai et al., 2005, Shoemaker et al., 2015). Beta-cells are the cells in the pancreas that produce insulin. Therefore the production and usefulness of ACE2 in some body systems cannot be over emphasized. Since ACE2 is expressed in the lungs, it makes this organ a primary target of COVID-19 infection via the inhalation of respiratory droplets. Thus, when their function is stopped or prevented by the virus, it will no longer be free to carry out the normal regulatory functions it is supposed to perform in the lungs as well as the pancreas, heart, kidney, liver and other tissues where ACE2 is expressed. This non-availability will also affect its ability to decrease the blood pressure. Therefore when these cells that produce ACE2 are destroyed through infection by the Coronavirus the organs and tissues expressing them tend to suffer due to the inability of the ACE2-expressing cells to function (Harrison, 2020). As there are several organs and tissues expressing ACE2 so also are the symptoms arising COVID-19. Information from some reports suggest that the most common symptoms include dry cough, headache, persistent high fever, pains in the muscle, not being able to breathe properly and hypoxia which may be followed by diarrhea and sometimes stroke (Guan et al., 2020, Vetter et al., 2020).

The major impacts of ACE2 in stabilizing the function of beta-cell and control of the pressure of the blood have already been stated, thus destruction of ACE2 by the virus highly increases the rate at which diabetic and hypertensive patients will come down with severe complications arising from COVID-19 (Sriramula et al., 2011, Fang et al., 2020). Several deaths arising from COVID-19 have been reported to be as a result of respiratory distress, as well as other conditions such as gastrointestinal disorders, meningitis, cardiac and pancreatic injuries which have been reported to be associated with COVID-19 infection (Moriguchi et al., 2020, Wang et al., 2020, Patel et al., 2020, Ying-Ying et al., 2020). Studies have shown that production of ACE2 is probably more in men than women, thus it is likely that men will suffer greater severe consequences as a result of COVID-19 than women (Sama et al., 2020, Wenham et al., 2020). Several persons are not at risk of the dire health challenges as a result of the infection, however, the ability to spread widely and usefulness of ACE2 seems to be a handicap for tissues that have already been weighed down by other serious health disorders, if the virus is able to get to such tissues (Harrison, 2020).

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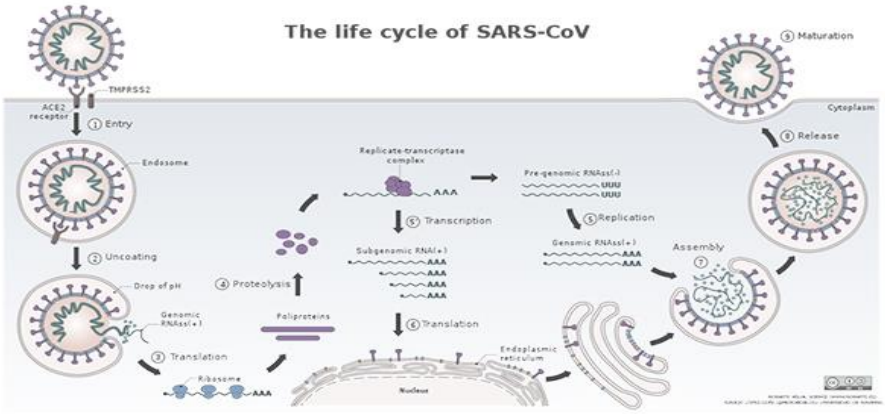

Figure 1: The infection cycle of SARS-CoV showing how the spike glycoprotein of the virus associates with ACE2 and gains entry into the host cell through endocytosis
Source: Harrison (2020)

3.2 Effect of SARS-CoV-2 on the human immune system

It is not very clear for now how the human immune system responds to SARS-CoV-2 infection, however, some studies have shown that individuals who eventually come down with serious secondary diseases as a result of COVID-19 have increased levels of pro-inflammatory molecules, such as interleukin-6 (IL-6) (Qin et al., 2020), and increased neutrophil-to-lymphocyte ratios. In such patients it has also been observed that there is a reduction in lymphocytes with a concomitant increase in the neutrophils number thus shifting the neutrophil-to-lymphocyte ratio (Tan et al., 2020, Qin et al., 2020). The virus finds its way into airway epithelial cells through ACE2 without the immune system recognising its presence in order to trigger certain antiviral interferon pathways (Vanderheiden et al., 2020) which usually act as the first line of defence in the event of a viral infection in the epithelial cells (Galani et al., 2017). Such epithelial cells that have been invaded go on to produce IL-6 and other compounds that are capable of promoting inflammatory reactions then mobilize neutrophils and other types of cells to where the infection has taken place (Harrison, 2020). It is important to note that the type III interferons provide the initial response to viral attack which is not inflammatory in nature (Pott et al., 2011). Therefore in animals where the type III interferon receptors have been disabled through genetic manipulations usually suffer from neutrophillia, injury to the lungs and death when infected by virus (Galani et al., 2017). Lymphocytes are a collection of immune cells, which are target specific in their actions, only responding to and destroying a specific antigen. Studies have shown that T cells are very useful in the removal of the virus from infected sites while neutrophils are employed in the defence from several common pathogens (Zhao et al., 2010, Montovani et al., 2011). Thus neutrophils can be referred to as being immunologically comparable to a blunt force weapon which still has the capacity to inflict serious harm on its target (Harrison, 2020). Out of the lymphocytes that remain during COVID-19, several of them exhibit a marker indicating exhaustion of the lymphocytes. This is called NKG2A. This therefore shows that they are no longer effective in putting up an effective defence during infection (Zheng et al., 2020). In fact, an increased neutrophil-to-lymphocyte ratio has been seen in several populations that can easily be infected by COVID-19 virus, which include the aged, diabetics, those with hypertension and morbid obesity (Valianthan et al., 2016, Sefil et al., 2014, Sun et al., 2017, Yilmaz et al., 2015). It is possible therefore that the virus could be worsening the already imbalanced immunological trends in these populations

(Harrison, 2020).
In a situation of healthy response (Tay et al., 2020), cytotoxic T cell (a type of lymphocyte) will arrive at the scene and may recognize and thus destroy the infected cell, which are then removed through phagocytosis by phagocytic cells that have also been moved to the site. However, in serious cases of COVID-19 it has been observed that IL-6 and interleukin 8 (IL-8) levels increase (Qin et al., 2020) which can quicken the exhaustion of the cytotoxic T cells, thus making them not to have enough strength to carry out their normal task (Zheng et al., 2020). IL-6 also does not allow the production of lymphocytes called 'peacekeeper', or regulatory T cells, which could also help to reduce a fast declining immune response (Kimura and Kishimoto, 2010). There has been a proposition that some death as a result of COVID-19 in patients is due to a swift but well directed strikes by some substances that promote inflammation called 'cytokine storm syndrome' (Mehta et al., 2020) that result in condition like cell-specific inability to fight infectious diseases, unprecedented neutrophil influx, severe and abrupt respiratory distress and failure of various organs (Harrison, 2020). There is also evidence indicating that the virus may be capable of infecting T cell lymphocytes directly through their spike proteins; the spike proteins join to small amounts of ACE2 produced on the membrane of the T cell (Wang et al., 2020). The virus does not replicate inside the T cells however; it is capable of killing them. Harrison (2020), therefore states that if this is true, then some T cells can be immobilized by naturally inherent warnings that emanate from other immune cells. It is also possible that they can be killed by the virus, causing lymphopenia which has been observed in most serious cases.

3.3 SARS-CoV-2 and BCG vaccination

BCG (Bacillus Calmette–Guérin) is a vaccine which was originally developed about 200 years ago at the Institut Pasteur, Paris to prevent tuberculosis. It is produced by live attenuation of *Mycobacterium bovis*, a related bacterial species to *M. tuberculosis* that causes tuberculosis. This vaccine has become the most administered vaccine worldwide after its development, with about 130 million children receiving the vaccine yearly (O'Neill and Netea, 2020). With the introduction of the vaccine, epidemiological studies indicated a reduction in infant mortality, in some cases up to 50%, which could not have been as a result of mare reduction in the rate of tuberculosis infection alone (O'Neill and Netea, 2020, Shann, 2010, Aaby et al., 2011). It is a known fact that viruses remain the major causative agents of respiratory tract infections in children. Thus this observed reduction in infant mortality by BCG could be as a result of the defence from unrelated infectious agents such as viruses which cause respiratory tract infections, and neonatal sepsis (O'Neill and Netea, 2020). Some clinical trials elsewhere have demonstrated that this proposition could actually be true, in some cases up to 70% reduction in respiratory tract infections was recorded (Stensballe et al., 2005, Wardhana et al., 2011, Ohrui et al., 2005, Nemes et al., 2018). Experimental studies to elucidate the mode of action by which BCG brings about the protective effects have been conducted by some workers using herpes simplex virus type 2, influenza A virus and vaccinia virus (Spencer et al., 1977, Starr, S. E. et al., 1976, Ikeda et al., 1985). In some of the experiments they discovered that the effect was brought about by macrophages in the peritoneal region (Ikeda et al., 1985), which strongly suggested that BCG had effects on the natural immune component of the host defence system. It has been found that healthy human volunteers administered with BCG vaccine had an increased production of cytokines involved in inflammatory reactions, like tumour necrosis factor (TNF), IL-1β and IL-6, when the monocytes obtained from these volunteers were stimulated outside of their bodies with unrelated disease causing agents (Kleinnijenhuis et al., 2012). These researchers found in the myeloid cells of the individuals who received the

vaccination that the increase in these compounds was followed by the reprogramming of the cells transcriptionally, epigenetically and metabolically (Kleinnijenhuis et al., 2012). The epigenetic changes usually manifest in the form of chemical alterations of the histone. These could be methylation and acetylation reactions, which result in increased accessibility of chromatin, make transcription of genes necessary in cells for responding to microbial attacks less difficult and also enhances the cell function (Netea et al,. 2016).

These observed changes that have occurred over long period of time in natural immune cell observable characteristics after administering BCG vaccine could be regarded as effective initiation of changes that may lead the cell to acquiring natural immune memory, and this has been called trained immunity. Thus there has been a proposal therefore that induction of trained immunity could be one of the mechanisms by which BCG vaccination prompts its defensive effects on individuals that received the vaccination. Thus BCG vaccination/administration leads to the formation of a population of monocytes and innate killer cells that have been trained epigenetically that usually resides in the bone marrow and when challenged with pathogens (bacteria or viruses), would lead these natural cells that defend the body against infections to display an increased response that will promote the host defence system. All these therefore indicate that trained immunity that is induced via BCG vaccination confers some effective and significant defence from several infections caused by viruses (O'Neill and Netea, 2020).

Based on the information already available it can be proposed that BCG vaccination may confer strong protection against infection by SARS- CoV-2 or it may significantly reduce the severity of COVID-19 disease (O'Neill and Netea, 2020). Recent studies relating the incidence of COVID-19 and BCG vaccination suggest that countries and regions that made it mandatory for BCG vaccination had reduced number of infections and lower mortality from COVID-19 (Gursel and Gursel, 2020), although the figures obtained may be affected by some factors such as demographic characteristics and genetic makeup of the population in the various locations where the study was conducted, differences in rate of testing individuals and the correctness of documentation of COVID-19 cases, and variations in the way by which the social distancing and quarantine in the various locations are implemented (O'Neill and Netea, 2020). During the lockdown period as a result of COVID-19 disease in Nigeria and several other African countries markets and transportation were operational. Also in these countries social distancing and wearing of face masks were not adhered to strictly yet the recorded death rates were much lower than expected considering the poor state of health facilities in these countries and the level of unpreparedness of the health officials. In Nigeria and these African countries BCG vaccination at birth is mandatory. Therefore it could be inferred that the vaccination offered some level of protection to the population. Hence the number of deaths recorded from the infection is low. Majority of the deaths were observed in patients whose systems have been weakened by comorboid conditions such as diabetes and high blood pressure. Thus it is worth exploring the possibility of using BCG or any other form of vaccination that can induce trained immunity as a useful tool to fight COVID-19, especially now that there is a pandemic which requires serious, reliable and competent strategies for restraining the spread of SARS- CoV-2 and also to contain the global epidemic. This can also be a viable tool that can be used against other emerging disease pathogens. There is however, need to test the hypothesis in clinical trials while we wait earnestly for the development of vaccine for SARS- CoV-2 which may take up to one to two years.

4.0 Conclusion and recommendation

It is necessary to note that our knowledge of the virus is still very low. Results and new data on COVID-19 keep emerging daily. Thus, the hypotheses and propositions will be refined and revised as more information is obtained. Meanwhile, everybody should continue to be mindful of the populations that are prone to the disease and there should be concerted efforts at conducting basic research aimed at increasing our understanding of the virus and the disease so as to enable early development of a vaccine as well as development of a standard treatment protocol.

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Nil

Declaration

Author(s) declare that this manuscript is an original article prepared by us which has not been sent elsewhere for consideration.

Authors contribution

Author 1: Conceptualized and wrote the original manuscript. Also took part in the review.
Author 2: Reviewed and formatted the manuscript.

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