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Mechanism of Antiviral Immune Response and COVID-19 Infection

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS designed the study. Authors AN and AML performed critical analysis of the literature. Author GMK analyzed the recent data updates. Authors AY and UM searched for the literature. Author AMH wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Immune systems are responsible for the body's protection against invading foreign agents that could bring harm to normal cellular activities. Viral infection is one of the significant foreign attacks on the body and the immune system has developed key mechanisms to contain such attack. The recent pandemic of the Coronavirus disease 2019 (COVID-19) has stimulated studies on antiviral response with much emphasis on the Corona viruses. This disease caused by the novel Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-COV-2) has been shown to have evolved with mechanisms to evade the normal immune responses. As such, this review therefore critically apprised recent literature on mechanisms of antiviral responses emphasizing on the Coronaviruses particularly the SARS-COV-2.The paper also highlighted the current situation regarding studies to find cure and vaccine development against the COVID-19.

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1. INTRODUCTION

The immune system is the major protective system of the body against invading foreign bodies and infectious agents [1]. Human immune system is one of the most critical and complex systems responsible for mediating response against foreign agents [2]. Such system could be the inborn innate immunity involving group of cells much organized up to organ levels that serve to protect the body against any infection. Such innate immune system involves one of the first line of immune response [3].

The innate immune system comprises of organs including the skin responsible for the major protection of the body [4]. Continuously, it includes group of cells protecting the body against any foreign invading material without any further categorization [4]. These cells mostly ferocious in their actions kill or damage the invading foreign body, release chemicals that ultimately kills the foreign agent [5].

Adaptive immunity on the other hand which is also referred to as the acquired immunity is the other type of immune response [6]. It is mostly concerned with detailed and more specific action against invading microbes, toxins and even mediating immune response between donor and recipient during organ or tissue transplants [7]. It is much controlled and specified form of immunity and involves key mechanisms for activation of different cells. This acquired immunity could mediate a cellular based response or humoral immunity [8].

Cell mediated immune response involves the activation of cells that could lead to destruction and elimination of the foreign bodies [9]. The cell mediated immune response comprises the key players; lymphocytes [10]. These cells particularly the T lymphocytes are responsible for the cell based immune responses. The T lymphocytes (T-cells) mediate response through presentation of the antigens of the invading cells particularly in viral infections [11]. The presentation involves action of proteins that culminates in formation of histocompatibility complex with the antigenic material. Accordingly, the presentation of histocompatibility complex class I (MHC I) leads to activation of Cytotoxic T cells [12]. These cells are significant in cell based immune responses. In essence, upon viral infection, the viral proteins are presented on the MHC I which in turn activates the cytotoxic T cells there by mounting a response against the virus [13].

Humoral immune response is associated with B lymphocytes activation and subsequent release of specially produced antibodies [14]. In terms of antigen presentation, the proteins of the invading agent are presented on MHC II thus leading to activation and subsequent proliferation of B-cells [12]. The B cells continue to produce antibodies otherwise known as Immunoglobulins and facilitation of Antigen-antibody complex formation [15]. This complex formation is paramount to elimination of the invading agent as the antibodies are specific towards the consequent antigen [16].

At the center of all these activations in the adaptive immunity are the Helper T-cells. They are referred to as architects of all immune responses [17]. The B-cells also develop into specialized Memory B-cells having the tendency to store the memory of the antigen which initially caused the immune response and subsequent production of the specified Antibodies [12]. With the current surge in the pandemic Corona virus disease-2019 (Covid19) which is ravaging the globe, this review critically discussed the current literature regarding antiviral immune response in humans with particular attention on the Covid19. Literature was extracted from Scopus, Web of Science, PubMed, and Embase using the following keywords; Coronavirus, Covid-19, Immune, Antiviral, Innate, Adaptive, Lymphocytes.

2. MECHANISM of DIFFERENT IMMUNE CELLS

Leucocytes or white blood cells are the cells responsible for immunity [18]. These cells have different actions and mechanisms from the onset of their activation to the consequent removal or destruction of the foreign invading agent [19]. The cells could morphologically be classified as granules-containing cells (granulocytes) and Non-granules contains cells (agranulocytes) [20]. Both cells depending on the invading agent particularly viral infections, mediate immune responses in various ways.

Granule-containing cells including neutrophils, basophils and eosinophils release the content of their granules which are mostly hydrolytic

enzymes that could easily destroy the invading agent [21].

The agranulocytes are do not contain granules. However, they are mostly capable of endocytosis, engulfing the invading agent and or its antigen there by causing its destruction [22]. Similarly, these cells including macrophages, monocytes, dendritic cells, natural killer cells, mast cells are also capable of releasing cytokines, interleukins and interferons which also cause the death and destruction of the invading agents [23]. These chemicals also play critical roles in B cells activation proliferation leading to secretion of different immunoglobulins [24].

3. ANTIVIRAL IMMUNE RESPONSES

Infections of viruses usually differ with other invading agents particularly in its mechanism and responses [24]. Retro viruses are able to enter into cells and utilize the cellular machinery to replicate its genome which at the final end will cause the destruction of the host cell [25]. Although there are systems that facilitate cellular recognition upon entry of invading foreign agents, viruses lack these specialized signals such as Pathogen associated molecular patterns (PAMPs) [26]. They could only be recognized with interaction of Toll-like receptors (TLRs) with their nucleic acids [27]. These interactions

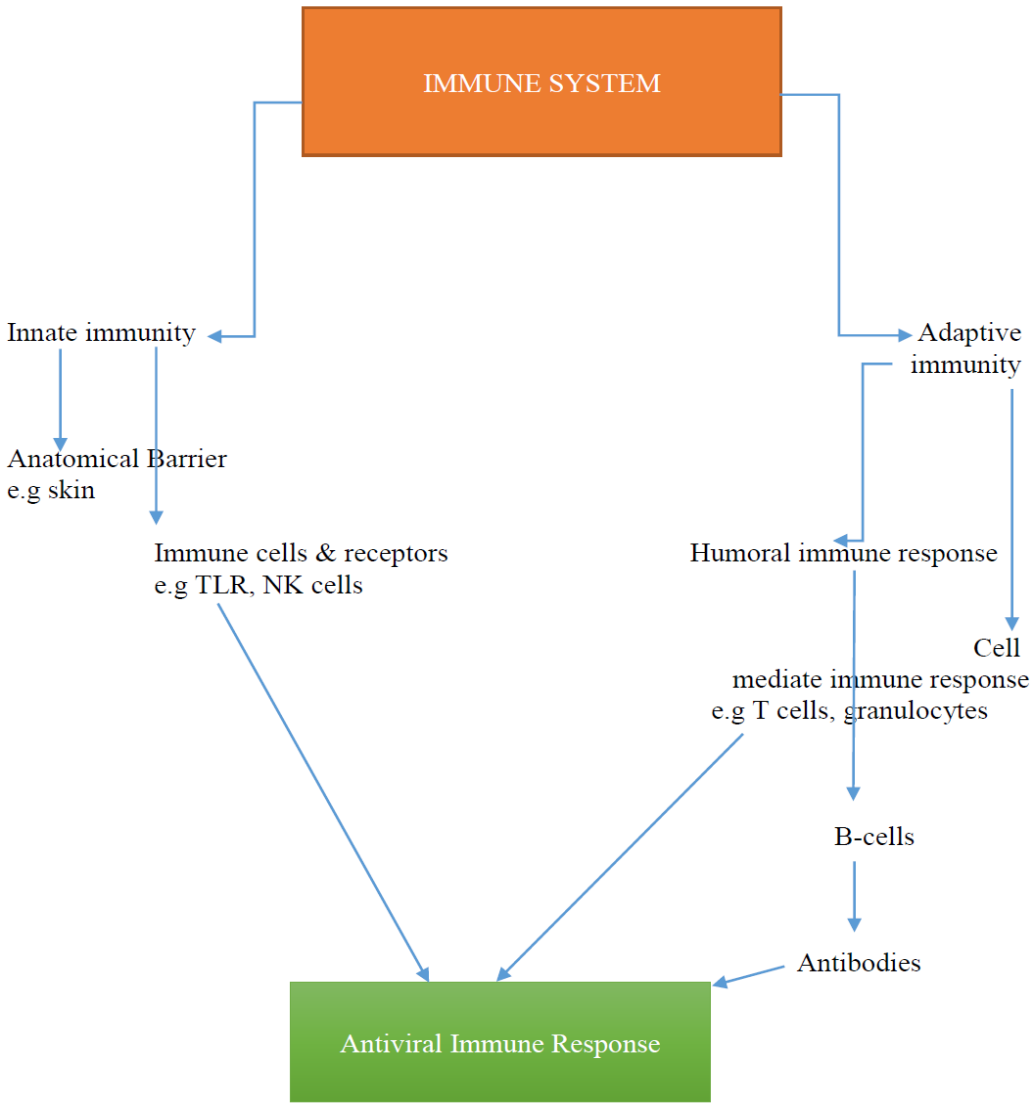

Fig. 1. Description of immune system and activation of antiviral immune response

between Toll-like receptors and the viral nucleic acids initiates a positive immune response via the release of interferons consequently mediating a B-cell mediated immunity with the concomitant production of Antibodies [26].

Viral infections have been associated with the type of the hosting system and nature of organs. Principally the nature of infection and mode of immune response could influence the pathogenesis of the disease [28]. Considering the respiratory system, it comprises the airways which are formed by a layer of epithelial cells which in essence is part of the innate immunity. Mucosal secretions by the epithelial wall serve also as part of the innate immunity. However, with a lot of viral population being part of the host microbiome particularly in the respiratory system, it may affect a possible antiviral immune response [29]. Similarly, various modifications during leucocytes differentiation might allow for lack of responses against the viral population in the microbiome. With that said however, no available studies have shown direct relation between onset of viral immune response and the microbiome in respiratory tract [30].

4. CORONA VIRUSES

Coronaviruses are members of a large family of viruses causing illnesses associated with respiratory tract. These viruses belonging collectively to the order *Nidovirales,* are positively stranded RNA viruses [31].

The coronavirinae are further subdivided into alpha, beta and gamma subfamilies each representing a particular nuclear configuration of the viral RNA [32]. The viral RNA contains a 5' cap and 3' polyA tail allowing to act as a messenger RNA for expression of its replication machinery proteins [31]. Thus a major part of the genome encodes for the replication machinery proteins hence its rapid replication upon entry into the host cell. Structural organization of the viral cell showed the virus as cylindrical with 4 specified proteins encoded by the minor sections of the genome [33]. These include the membrane (M) protein, the Spike (S) protein, Envelop (E) protein and Nucleocapsid(N) protein.

A major distinction is seen in the beta subfamily where another (5^{th}) structural protein is observed, the Hemagglutinin esterase protein [31]. The protein is thought to enhance spike protein activity and establish interaction with sialic acids on glycoproteins present on the surface of host cells there by facilitating viral entry [34].

Upon viral entry, the expression of the replication machinery is achieved. The Replicase protein expression is achieved in a series of complex mechanisms starting with expression of two polyproteins ppla and pplb [31]. Studies showed distinct controlled mechanisms in expression of these proteins suggesting the complicated nature of the replication machinery expression which powers the virus with its rapid spread [35]. Next is the assembly of the viral replication complex to replicate the Viral RNA.

The replication machinery utilizes viral RNA to synthesize the viral genome again. The viral RNA synthesis proceeds with formation of Genomic RNA and the sub genomic RNA which is concerned with expression of structural and accessory proteins. Their encoding genes are located along the 3' terminal end representing nest of RNA [36]. The process is completed with translation of the structural proteins of the virus which are then transferred to the Endoplasmic Reticulum, assembled and further released as mature varions.

5. COVID-19

The Corona virus disease-2019 was reported to be caused by a new strain of SARS-CoV2 in December 2019 [37]. Patients have shown pneumonia like symptoms and others associated with severe respiratory syndrome [38]. According to WHO, the massive spread of COVID-19 has reached more than 10 countries globally and could possibly infect 20 million people.

As at March 2020, there have been 274,202 reported cases for Covid-19 out of which 11,354 deaths have been reported. Positively, about 90,000 individuals have completely recovered and for the first time no new indigenous case has been recovered in the Chinese city of Wuhan where it started. In Nigeria, so far 135 cases have been confirmed with 2 deaths most of which have been from individuals with history of foreign travels [39]. Measures have already been in place by various government agencies to contain and control the spread of the virus.

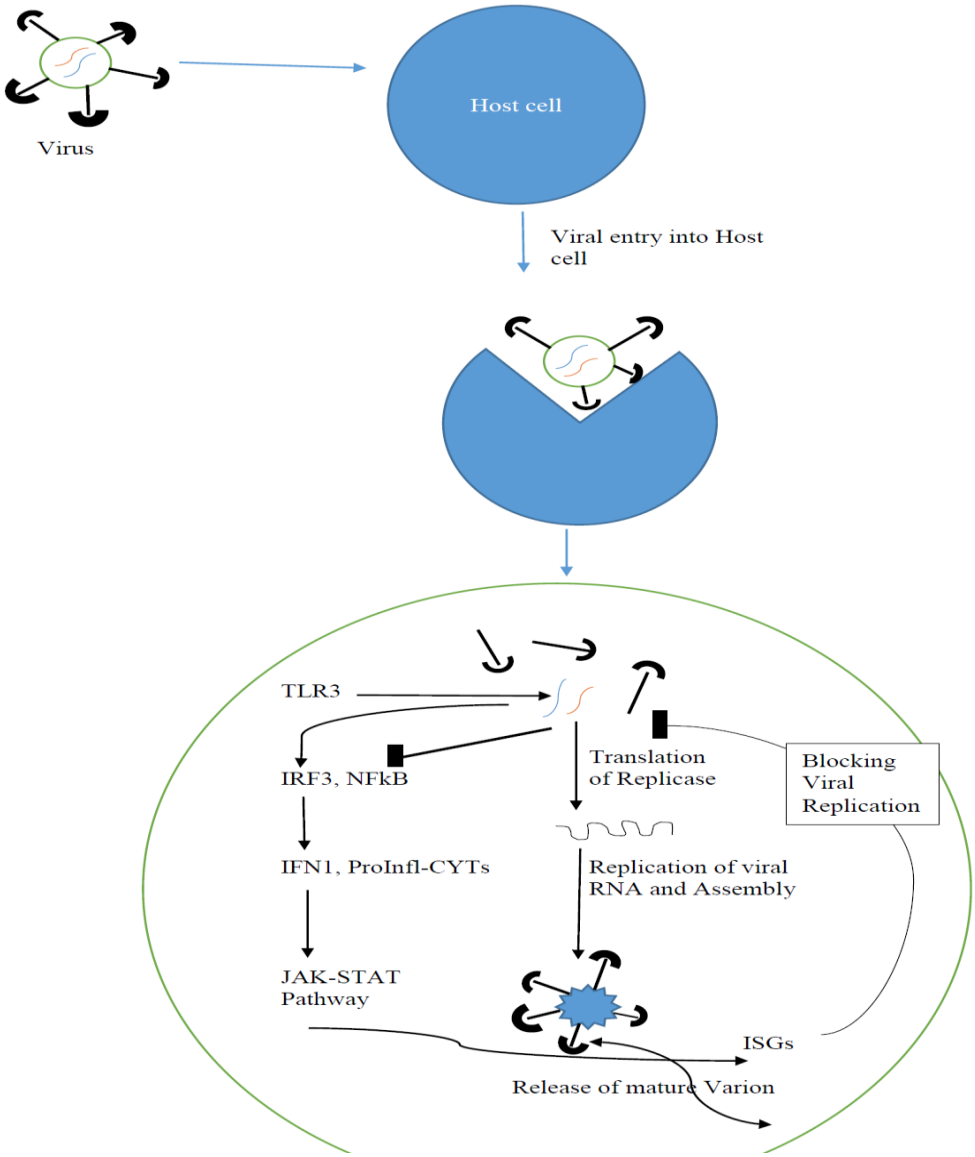

Fig. 2. Summary of life cycle and pathogenesis of SARS-CoV2; the viral proteins together with yet to be elucidated mechanisms inhibit activation of transcriptional factors IRF3 and NFkB. These factors initiate a signal cascade that results into blocking of viral replication and assembly (adopted from [5])

Key molecular mechanisms of the SARS-CoV2 pathogenesis are still unknown [40]. However, its pathophysiology involves viral entry in respiratory droplets into the lungs via the airways [31]. Major target of the virus is the alveolar cells which play critical roles in gaseous exchange during respiration [41]. Interaction between the viral Spike proteins and the ACE receptor ensures viral entry into the alveolar cells with the concomitant of structural disintegration. The Inflammatory response initiated was due to release of pro-inflammatory cytokines such as IL-6 and TNF-alpha [37]. These two cytokines interact with the brain's hypothalamus resulting in physiological changes including increase in body temperature and fever. Additionally, the response results in vasodilation and increase vascular permeability. As such, with corresponding fluid accumulation, causing increased breathing capabilities and by extension breathing difficulty [31].

As it is currently no specified treatment or vaccine for Covid-19 [42]. However, various clinical trials have been conducted and have shown significant results. The United States'

Food and Drug administration has shown promising results regarding the use of the anti-malarial drug chloroquine and its derivative as possible treatment for Covid-19 [41]. However, the FDA is yet to give a formal approval contrary to previous claims. Possibly, target in development of treatment include study on molecular mechanism of the disease pathogenesis to target the viral key proteins [42]. However, as such processes could take longer period, the rapid spread of the disease may not allow for that.

6. HOW DOES SARS-COV2 POSSIBLY EVADE ANTIVIRAL IMMUNE RESPONSE?

The SARS-COV2 is a novel corona viral strain responsible for the December 2019 pandemic. The key mechanisms through which these coronaviruses including the SARS-CoV2 tries to circumvent immune response are still under investigation [36]. However, as with most coronaviruses, the SARS-CoV2 utilizes its structural proteins to gain entry into the host cell cytosol as well as suppress signaling pathways particularly with the Toll-like receptors (TLR) [31]. Usually, the interaction between the viral nucleic acid is with TLR7 and TLR3 [27]. This interaction initiates a signal cascade involving the transcriptional factors IRF3 and NFkB.

These transcriptional factors are further translocated into the nuclei where they activate the machinery for expression of Pro-inflammatory cytokines and interferons particularly IFN1 [33]. IFN in turn activates the JAK-STAT pathway via phosphorylation of STAT-1 and -2. The combine activated forms of STAT-1 and -2 further form complexes with IRF9 with the immediate release of active Interferon stimulating genes (ISGs) resulting in a massive suppression of viral replication [33].

7. CONCLUSION

The Covid-19 pandemic has so far reached a very disturbing rate. Measures have continued to be in place to prevent the continued spread of the virus, and so far there have been promising results. Researchers have continued to investigate the mechanism of antiviral response to the SARS-Cov2 and there have been positive results. Moreover, there is hope that in the near future, vaccine and definitive treatment to Covid-19 will come to fruition.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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