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# Coronavirus Disease (COVID-19) Infection and Innate Immuno-Response: Pathway to Eradicating the Pandemic

**Ekom Ndifreke Edem[1]*, Anthony Nathaniel Umo[2] and Udeme Olayinka Olaniyan[3]**

[1]Department of Medical Microbiology, University of Uyo Teaching Hospital, Uyo, Nigeria

[2]Department of Medical Microbiology and Parasitology, College of Health Science, University of Uyo, Nigeria

[3]Department of Environmental Health, American University of Beirut, Lebanon

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***Corresponding author:** Ekom Ndifreke Edem, Department of Medical Microbiology, University of Uyo Teaching Hospital, Nigeria, Email: ekomedem@gmail.com

## Abstract

Covid-19 infection is highly transmissible with high degree of hospitalization and few level of lethality which has raised great concerns globally. Covid-19 is acquired through exposure to microdroplets present in exhalates of individuals already infected or by surface contact with contaminated formites with the viral particle and once the viral particle reaches the bronchioles and alveolar spaces; it binds to cells of the bronchial epithelium and Angiotensin 2 Converting Enzyme (ACE2) of the alveolar. An immense understanding of the interaction between Covid-19 infection and the host immune system could be the breakpoint needed to provide better management, treatment and support for the disease sufferers. Therefore, review of current knowledge between Covid-19 infection and the host innate immune system is important in order to sufficiently understand its pathogenesis and further give clues for the clinical management and development of preventive therapeutic strategies in treating this infection.

**Keywords:** COVID-19; WHO; Medical Treatments; Humans

## Introduction

The infection was named COVID-19 and the virus as SARS-CoV-2 by WHO on February 11, 2020 [1]. SARS-CoV-2 is of the family Coronaviridae [2], with a large number of species which infects various wild animals and some also affects human beings [3,4,5]. Majority of COVID-19 cases (about 80%) are asymptomatic or exhibits about 20–30% of mild common cold-type to moderate symptoms, but approximately the 15% progresses to severe pneumonia and about 5% eventually develops acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure which requires hospitalization at ICU for assisted respiratory support and other medical treatments until recovery, or possibly death [2,6,7,8]. The most common symptoms of COVID-19 are fever, fatigue, and respiratory symptoms, including cough, sore throat and shortness of breath [6, 9].

The SARS-CoV-2 enters the human host through exposure to its microdroplets present in the exhalates from an infected individual or by contact with the viral particle present in contaminated fomites [2]. The virus binds to cells of the bronchial epithelium and the type-II ACE2+ pneumocytes of the alveolar epithelium using the Angiotensin 2 Converting Enzyme (ACE2), a metallopeptidase present on the membrane of many cells, including type-I and -II pneumocytes, receptor [10, 11]. The early defense mechanism in an infected cell is the production of type-I and type -III IFN [12, 13]. Viral interactions with the innate immune system play a central role in determining the outcome of infection. Early control

of viral replication by type I interferons (IFN), complement proteins, and other innate immune mediators limit viral spread within the host during the early phases of the disease [14]. However an overactive innate immune response can result to tissue damage [15]. However, the importance of this review is to analyze the main aspects of the innate immune response against SARS-CoV-2.

## SARS-Cov-2 Receptors, Attachment and Replication

SARS-CoV-2 is mainly considered to infect respiratory epithelial cells, but a recent study confirmed that it can also infect T lymphocytes, spleens, and lymph nodes [16]. Penetrating the target cell is a crucial point for replication to occur but the primary marker in the replication cycle of SARS-CoV-2 is an adequate attachment of the S glycoprotein to a cell surface receptor [17,18]. The S protein is used by SARS-CoV-2 to gain entry into human cell and bind to the angiotensin-converting enzyme 2 (ACE2) via cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin as priming stage [19]. Priming activates the S protein to intercede the fusion among the viral and cell membranes, leading to discharging the nucleocapsid into the host cell [20-22]. However, the S glycoprotein includes two subunits, S1 and S2, S1 is responsible for the determination of the virus-host range and cellular tropism via Receptor Binding Domain (RBD), while S2 facilitates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) and heptad repeats 2 (HR2) [23]. The Angiotensin-converting enzyme 2 (ACE2) is an essential component of the renin-angiotensin system [24] which binds to the S protein of coronaviruses [25] and also a receptor of SARS-CoV-2 [26] for entry into humans [27]. Analysis of the receptor binding motif (RBM), a portion of the receptor binding domain (RBD) that makes contact with ACE2 Li W, et al. [28], revealed that most amino acid residues essential for ACE2 binding were conserved in SARS-CoV-2. Host proteases mediate the activation of S protein, for example, activation of S protein of SARS-COV-2 requires further cleavage by the endosomal cysteine protease cathepsin L and another trypsin-like serine protease [29-31]. Furthermore, S protein of SARS-CoV-2 encompasses two cleavage locations for furin which is a ubiquitously expressed protease [32].

The genomic RNA of coronavirus of approximately 30,000 nucleotides encodes structural proteins and nonstructural proteins of the virus that have a critical role in viral RNA synthesis (called replicase-transcriptase proteins). At least one niche-specific protein, nonstructural protein 2 (nsp2), and one structural protein, the nucleocapsid protein (N), are involved in viral RNA synthesis. The expression of the coronavirus replicase-transcriptase protein genes is mediated by the translation of the genomic RNA. The replicase-transcriptase proteins are encoded in open-reading frame 1a (ORF1a) and ORF1b and are synthesized initially as two large polyproteins, pp1a and pp1ab. The synthesis of pp1ab involves programmed ribosomal frameshifting during translation of ORF1a. During or after synthesis, these polyproteins are cleaved by virus-encoded proteinases with papain-like (PLpro) and chymotrypsin-like folds into 16 proteins. NSP1 to NSP11 are encoded in ORF1a, and NSP12 to NSP16 are encoded in ORF1b. The replicase-transcriptase proteins, together with other viral proteins and, possibly, cellular proteins, assemble into membrane-bound replication-transcription complexes (RTC). These complexes accumulate at perinuclear regions and are associated with double-membrane vesicles. Hydrophobic transmembrane domains are present in NSP3, NSP4, and NSP6 likely serve to anchor the nascent pp1a/pp1ab polyproteins to membranes during the first step of RTC formation. Finally, the virion-containing vesicles fuse with the plasma membrane of the cell to release the virus. The virus then attaches a new cell, and the cycle is repeated [23].

## SARS-Cov-2 and Innate Immune Response

The innate immunity is a well-maintained defense mechanism for accelerated recognition and control of pathogens [33]. During viral infections, after viruses enter the host cells, they are recognized by Pattern Recognition Receptors (PRR) such as TLR7 and TLR8, RIG-I-like (RLRs), NOD-like receptor (NLR), C-type lectin-like receptors, and free-molecule receptors all expressed by epithelial cells as well as by local cells of the innate immune response, like alveolar macrophages [34,35], through the pathogen molecular patterns (PAMPs). Following the promotion via PAMPs, PRRs recruit adaptor proteins that comprise complex signaling pathways involving several kinases [36], which activates crucial downstream transcription factors, including interferon regulatory factor (IRF), NF-kB, and AP-1, resulting in production of the Type-I and -III antiviral Interferons and different chemokines [37]. This signaling pathway eventually results in the promotion of the essential transcription factors, such as the nuclear factor interferon regulatory factor 3 (IRF3), Nuclear factor-kappa B (NF-κB), and Activator Protein-1(AP-1) [38] which attracts more innate response cells [polymorphonuclear leukocytes, monocytes, NK cells, dendritic cells (DC)], which also produce chemokines, such as MIG, IP-10, and MCP-1, capable of recruiting lymphocytes, which in turn, will recognize the viral antigens presented by DCs [13,39]. Synergistically, these agents release type I interferons that are secreted and act nearby interferon α/β Receptor (IFNAR) [40]. The antiviral effect of interferon type I has interfered through different mechanisms [41]. SARS-CoV-2 can infect type-I and -II pneumocytes, plus alveolar macrophages [42]. Interestingly, SARS-CoV-2 induces only five cytokines (IL-6, MCP1, CXCL1, CXCL5, and CXCL10/IP10)

[2]. Additionally, chemokines and cytokines are ordered to stimulate inflammatory reactions, which are responsible for extensive tissue damage [38]. Blanco-Melo, et al. [43] studied the transcriptional response to SARS-CoV-2, in *invitro* infection of respiratory cell lines, experimental *invivo* infection of ferrets, and post-mortem lung samples of COVID-19 patients. Their results show that SARS-CoV-2 induces a particular signature characterized by reduced IFN-I and IFN-III responses and significant induction of multiple proinflammatory chemokines, IL-1B, IL-6, TNF, and IL1RA. These findings were further supported by the increased serum levels of these molecules in COVID-19 patients. SARS-CoV-2 differs from other coronaviruses in its capacity to replicate within the pulmonary tissue, elude from the antiviral effects of IFN-I and IFN-III, activate innate responses, and induce the production of the cytokines required for the recruitment of adaptive immunity cells. Furthermore, patients needing ICU care have raised plasma levels of several innate cytokines to include IP-10, MCP-1, MIP-1A, and TNFα [6]. Overall, the robust innate immune response toward viral infection relies profoundly on the interferon (IFN) type I responses and its downstream cascade that completes in managing viral replication and initiation of the effective adaptive immune response [44,45].

## Macrophages Responses to COVID-19 Infection

Macrophages are critical producers of type I interferons and other pro-inflammatory cytokines which trigger antiviral protection, even though they potentially contribute to immune pathology mediated to viral infections [46]. The role of macrophages can be inferred from the immune response observed in other coronavirus infection. SARS-CoV has an accessory protein, Open Read Frame 8 (ORF-8) [47]. This protein determines the activation of intracellular stress mechanisms, lysosomal damage, and activation of autophagy. Specifically, at a macrophage level, ORF-8 causes intracellular aggregates that interact with NLRP3, also called Cryopyrin, a structural protein of the inflammasome, determining its activation [48]. The Inflammasome is a multiprotein complex, part of the innate immune system, responsible for the activation of inflammatory response. Inflammasome activation recruits pro-caspase-1, a proteolytic enzyme that cleaves proinflammatory cytokines, such as pro-IL-1 β and pro-IL18, thus activating them. This leads to a particular form of programmed cell death, which is called pyroptosis, in which the cell, following recognition of intracellular pathogens, undergoes programmed cell death associated with discharge of inflammatory cytokines, chemokines, and subsequent chemotaxis of inflammatory cells. In particular, the release of IL18 stimulates the production of IFN gamma, which determines the development of TH1 polarization, contributing to the development of adaptive immunity [49-52]. It is plausible that it occurs similarly in SARS-CoV-2 infection since studies on SARS-CoV-2 genome prove that there is a high analogy with the SARS-CoV ORF-8 region, so we may suppose that macrophage activation of the inflammasome plays an important role determining the important inflammatory response observed in patients with more severe forms of infection [53,54]. Interleukin 1 released by macrophage through the inflammasome contributes to the cytokine storm responsible for the most aggressive forms of COVID-19, with symptoms of hyperactivation of the immune system similar to secondary forms of hemophagocytic lymphohistiocytosis, (sHLH) infection [55]. The pathogenetic role of IL1 could lead to important therapeutic implications. Acting on the inflammatory signaling pathway induced by the inflammasome, Anakinra, a recombinant IL-1 receptor antagonist, could block the cytokine storm, similarly to various secondary HLH conditions [56]. Several case reports evaluated the effectiveness of Anakinra in refractory forms of COVID-19 pneumonia. In a case series of 9 patients treated with subcutaneous Anakinra, there was only one case of failure, while the other 8 had improvement in clinical conditions and reduction of oxygen flow and blood inflammation markers [57]. Nowadays there are already 13 clinical trials registered on ClinicalTrials. gov investigating the efficacy of the inhibitor of IL-1-RA Anakinra alone or compared with other drugs [13].

## Dendritic Cells and COVID-19

Dendritic cells and macrophages are first line components of the innate immune network. DCs, which can be grouped into plasmacytoid (pDC) and myeloid types (mDC), play important roles in driving both innate and adaptive immune responses to viral pathogens [58,59]. pDCs rapidly respond to viruses or their derivatives to produce large amounts of type I IFN, which can induce direct antiviral responses and also modulate other components of the innate and adaptive immune response, such as natural killer cells and CD8 T cells. mDCs can also secrete large amounts of type I IFN.

## COVID-19 and Neutrophils

The complete blood count during COVID-19 infection is frequently performed, and an increase in neutrophils with lymphopenia is observed. However, from an anatomopathological point of view, some case series of patients who died from COVID-19 show a marked infiltration of neutrophils in patients' lungs [60]. However, polymorphonuclear cells (PMN) infiltrate the lung during Covid-19 infection. They also contribute to the healing process through clearance of the virus and production of growth factors involved in healing and re-epithelialization of damaged regions [61]. According to Channappanavar, et al. [13], viral infection, leading to the expression of viral proteins and local damage at the epithelial cells, leads to

the PMN cells infiltration. PMN cells contribute to local production of cytokines and chemokines; in particular, the interaction of PMN cells with lung cells amplifies this effect. In vitro work demonstrated that PMN cells, when they are linked with type I epithelial alveolar cells (AT1) infected with coronaviruses, had an increased expression of mRNA levels of proinflammatory cytokines (IL-18, IL-1a, IL-1b, and TNF-a), CXC chemokines (CXCL-1, CXCL-2, IP-10, and CXCL-11), and CC chemokines (CCL- 2, CCL-4, CCL-7, CCL-9, CCL-12, and CCL-22) [62]. So, their role would appear dichotomous; on the one hand, neutrophils can play as actors in the early recruitment of inflammation cells; on the other, they can contribute to tissue damage when their action does not appear to be adequately counterbalanced [59]. Furthermore, increased neutrophils and diminished lymphocytes also associate with the disease severity and mortality in COVID-19 patients [9]. Lymphocyte antigen 6 complex locus E (LY6E) has been shown to interfere with SARS-CoV-2 spike (S) protein-mediated membrane fusion [63].

### COVID-19 Interaction with Complement System

The complement system has a critical function in immune responses to infection caused by the SARS-CoV-2 because it enables the detection and response to viral particles. Considering its potency to harm the host tissues, the complement system is regulated via inhibiting proteins of serum. C3a and C5a show a proinflammatory activity that could initiate the recruitment of the inflammatory cell, such as activation of neutrophil cells [64]. Activation of complement and the contact system, through the formation of bradykinin, may perform a role in the SARS-CoV-2-induced pulmonary edema, and it's recommended that further work is necessary to verify the information [33]. The complement system doesn't seem to be protective of SARS-CoV-2 even when it is sufficient enough in defending against various viruses.

### Covid-19 Interaction with Interferons

Interferons mediate direct antiviral influences that restrict viral replication via activating/regulating a group of welldefined antiviral effectors, such as protein kinase R (PKR) and Ribonuclease L (RNase L), while inflecting other facets of the innate and adaptive immune responses via stimulating a wide variety of interferon-inducible genes [65]. Interferons (IFN) have important roles in the inhibition of viral replication, through different effector proteins [66,67]. There are three types of interferons, Type I (interferon α β), Type II (Interferon γ), and Type III (Interferon λ) [68]. Although all three are likely to be involved in protection from coronavirus infection, type I IFN is the most studied in this area and his role appears predominant especially in the early stages of the infection [69], especially restricting virus replication before adequate adaptive immunity is mounted [70]. Interferons I and III are cytokines with critical roles in the innate immune response against viral infections [71]. Virus-infected cells induce and secrete interferon I molecules that bind to the cell surface receptor IFNAR (interferon III uses a different receptor), thereby triggering the Jak-Stat (Janus kinase/signal transducer and activator of transcription) signaling pathway that switches on many antiviral genes. The interferon-stimulated genes are then transcribed into RNA and translated into proteins that suppress viral replication and spread [72]. There are two main pathways via them host cells sense invading viruses and trigger the interferon pathway; the cytoplasmic interferon induction pathways and TLR associated pathway (Samuel, 2001). TLRs including TLR3, TLR7, TLR8 as well as TLR9 could recognize viruses in endosomal compartments as they penetrate cells [73]. In contrast, cytoplasmic caspase activation and recruitment domain (CARD) RNA helicases, RIG-I, and melanoma differentiation-associated gene 5 (Mda5), identify viral RNAs in the cytoplasm [74].

The production of type I IFN is enhanced by viral RNAs trough two cytosolic proteins: RIG-1 (retinoic acid-inducible gene I) and MDA5 (melanoma differentiation-associated protein 5). The recognition of viral RNA by these cytosolic receptors leads to the activation of IRF3 and determines the initiation of the transcription of type I IF, thus contributing to resolution of the infection [75]. SARS-CoV-2 have several proteins, including nsp1, nsp3, nsp16, ORF3b, ORF6, and M and N proteins, similar to proteins of other coronaviruses, which act on type I IFN pathway, either by inhibiting transcription or by acting on effector mechanisms [69,76,77]. SARS-CoV-2 robustly triggers the expression of numerous IFN-inducible genes (ISGs) [33]. These ISGs display immunopathogenic potentials, defined by the overrepresentation of genes implicated in inflammation [78]. However, SARS-CoV-2 does not induce types I, II, or III interferons in the infected human lung tissues [42], as cytokine storm may be the main cause for the severity of the coronavirus infection [27]. Although, type I/III interferons (IFNs) are considered the most important for antiviral defense. Early evidence demonstrated that SARS-CoV-2 is sensitive to IFN-I/III pretreatment in vitro, perhaps to a greater degree than SARS-CoV-1 [43].

## Conclusion

The knowledge about COVID-19, including replication of the virus, cell biology, and pathogenesis, is slowly increasing. Innate immunity, acting as the first element of defense, can represent, together with other mechanisms, a promising target for the treatment of patients or at least to better understand the pathogenesis of the disease [79-82]. Although there is an impressive speed by which COVID-19

was identified, and the genome was sequenced, along with the earlier accumulated data on the other members of the corona-virus family, which had provided a lot of new insight about this universal health issue [83-88]. There are still many significant and intriguing aspects remaining to be identified about COVID-19 and future directions for COVID-19 studies are open and more studies on clarifying the immune reactions that occur during this infection so as to lead towards probable vaccine development and antiviral drugs are required.

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