Biological Times

Volume No. 3 | Issue No. 8 | Pages 3-4

Unraveling the Frontline Defense: Innate Immune Response to SARS-CoV-2 Infection

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ABSTRACT

The Coronavirus disease 2019 attained a pandemic status on March 11, 2020. The Coronaviruses devise immune system gears to target multiple aspects of innate immune system. Acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) to prompt cytokine storm, prejudice interferon response and abolish presentation of antigen by Class I and Class II MHC molecules. By understanding the recognition of SARS-CoV-2 and its immune evasion from immune system will probe into a new perspective of viral clearance, vaccine formulation and immune therapeutic pattern and assessment. This review confers the connection of host innate immune response and immune evasion strategies of corona virus infection.

Keywords: Immune response, Neutrophils, Immune evasion, corona virus, vaccination

Introduction

Coronavirus is originated from the city of China named Wuhan and spreading to the rest of the world. In Pakistan till 09/09/2020 around 299,659 cases were confirmed against COVID-19 out of which 286,506 were recovered along with 6359 deaths (NCOC, Pakistan). In January 2020, World Health Organization (WHO) named this virus as 2019 novel coronavirus (2019-nCoV) which is also called as SARS-CoV-2 that is the cause of COVID-19 (1).Infection with corona virus show a clinical symptoms like mild influenza, severe pneumonia and acute respiratory distress syndrome. Fortunately, in Pakistan number of cases have been reduced due to smart lock down policy by the Government. This article scrutinizes the normal innate immune response against coronaviruses and their immune evasion strategies in the host along with the virus morphology, its classification and a brief history of viral pandemic.

NSPs	Amino acids	Function	Reference
NSP1	180	Suppress antiviral host response	(6)
NSP2	638	Unknown	
NSP3	1945	NSP3 Papain like protease (PLpro)	(7)
NSP4	500	Complex with NSP3 and NSP6	
NSP5	306	3-Chymotrypsin like protease (3CLpro)	(8)
NSP6	290	Complex with NSP3 and NSP4	
NSP7	83	Complex with NSP8: Primase	
NSP8	198	Complex with NSP7: Primase	
NSP9	113	Viral genomic RNA reproduction	
NSP10	139	Complex with NSP14: replication fidelty	(9)
NSP11	13	Short peptide at the end of ORF1a	
NSP12	932	RNA dependent RNA polymerase enzyme (RdRp)	
NSP13	601	Helicase enzyme	
NSP14	527	Exon: 3′–5′ exonuclease,	
NSP15	346	XendoU: poly(U)-specific endoribonuclease	
NSP16	298	2′-O-MT: 2′-O-ribose methyl transferases	

History

Severe acute respiratory syndrome (SARS) infections had emerged in Wuhan city of China with pneumonia like symptoms in December 2019.After thorough investigation by Chinese laboratories, it was identified as novel coronavirus (nCoV) (2).After detailed research on respiratory samples revealed a novel virus and SARS-CoV-2 name was given to this newly reported virus by International Committee on Taxonomy of Viruses (ICTV). The World Health Organization (WHO) announced it as COVID-19 on February 11, 2020, and then declare it as world pandemic concerning the public health emergency internationally. Corona viruses are very important pathogens as they spread from animals-to-humans and from human-to-human. Coronaviruses such as SARS and Middle East Respiratory syndrome (MERS) were reported in China in 2003 and 2012, respectively (3). The sign and symptoms of SARS-CoV-2 such as dyspnea, discomfort in respiratory tract, fatigue, dry cough, and diarrhea and in severe cases multiple organ failure and high cytokine-storm driven sepsis are noticed and the same signs were seen by SARS in 2003-2004 and MERS coronaviruses infections in 2012.

Classification and morphology

Coronaviruses are classified in order *Nidovirales*, family *Coronaviridae* and subfamily *Coronavirinae.* There are four genera in this genus named as Alphacoronavirus (229E & NL63 strains), Beta coronavirus (OC43, HKU1, MERS & SARS), Gamma coronavirus (includes viruses of whales and birds), and Delta coronavirus (viruses isolated from pigs and birds) (4).

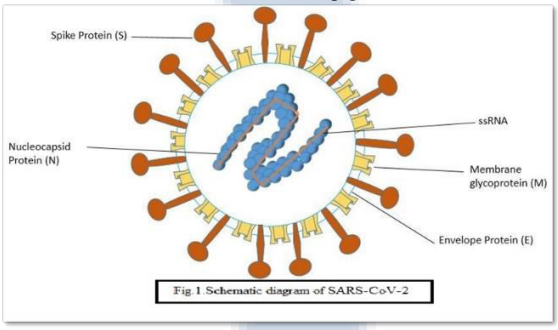

Fig.1 Schematic diagram of SARS-CoV-2

The recent outbreak of corona virus (Beta coronaviruses) shows 88% genetic similarity to SARS viruses that were isolated in 2018 from the bats in eastern China. In human four types of coronaviruses cause infections including 229E, NL63, OC43, and HKU.SARS-CoV-2 under electron microscope looks like roughly, spherical and pleomorphic with club shaped projections formed by spike (S) proteins with an envelope that contains positive sense single stranded RNA (+ssRNA) of 30kb approximately. This genome acts as messenger RNA (mRNA) containing 5' terminal cap with 3' poly A tail structure (5). Besides spike (S) protein, virion also contains envelope (E), membrane (M) and nucleocapsid (N) structural proteins as shown in figure 1. Corona virus is like crown or solar appearance due to spike proteins attached to the double layer lipid envelope and its nucleocapsid contains about 29,903 nucleotides. The phylogenetic analysis indicates the close resemblance of the virus up to 89.1% with SARS of genus Beta coronaviruses and subgenus Sarbecovirus. There are typical nucleotide sequences at the terminal ends of SARS-CoV-2. It contains about 265 nucleotides at the 5' end and 229 nucleotides at 3' end which is typical for beta coronaviruses. There are sixteen non-structural proteins coded by open reading frame (ORF1a & ORF1b) which is 2/3 of the viral genome. Two polypeptides are produced due to frame shift between these ORFs. The viral structural proteins including spike, envelope, membranes and nucleocapsid contain 3822, 228, 669 and 1260 nucleotides in length, respectively. The NSPs perform different functions which are assembled in Table-1.

Virus entry mechanism

The spike glycoproteins of coronaviruses when bind with angiotensin converting enzyme 2 (ACE-2) over expressed cells start life cycle of SARS-

To cite this article: Hayat D, R Ahmad, MA Haneef, A Nawaz & S Seher. Unraveling the Frontline Defense: Innate Immune Response to SARS-CoV-2 Infection. Biological Times. 2024 August 3(8): 3-4

CoV-2. After receptor binding, viruses induce some conformational changes in host cell membranes or enter through endocytosis. Inside highly acidic endosomal pH environment, uncoating of viral envelope occurs. Finally, there is release of viral genomic RNA into the cell cytoplasm and encodes for NSPs. Viral proteins are also produced due to encoding of sub genomic mRNA by polymerase. Meanwhile, Golgi apparatus and endoplasmic reticulum together assembles the newly formed genomic RNA, envelope, nucleocapsid and glycoproteins inside the vesicles and the virion fuses with plasma membrane and released outside. The coronaviruses again bind with the ACE-2 bearing receptor cells of the organs like intestines, heart, kidneys, mouth, lungs, esophagus and bladder as shown in Fig. 2.

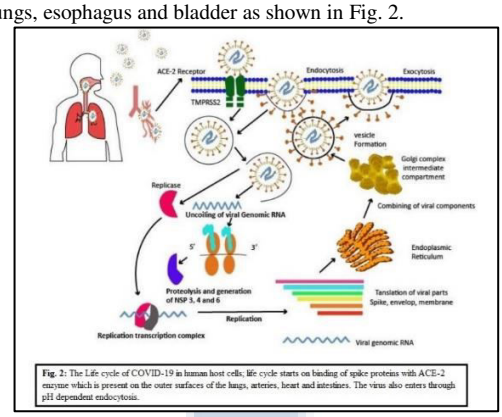

Fig. 2: The Life cycle of COVID-19 in human host cells; life cycle starts on binding of spike proteins with ACE-2 enzyme which is present on the outer surfaces of the lungs, arteries, heart and intestines. The virus also enters through pH dependent endocytosis.

Innate immune responses against COVID-19

The human body immune system is a strong defensive tool to protect the body from the harmful effects of invading pathogens. As we know the emergence of coronaviruses which a new particle to which our body's immune cells is are not familiar. As far as the foreign pathogen gets entry inside the body, our immune cells get activated to kill the foreign antigen (10). The immune cells are equipped with specialized mechanisms to recognize, process and kill the foreign antigens prior to its multiplication for causing the disease. The human body has two types of immunity against pathogens, one is innate immunity which is present by birth in every individual and it is non-specific resistance of the host and second is adaptive immunity which is the specified host immune response. The innate immunity is actually comprising of 1st line and 2nd line of defense which includes the components such as normal microbiota, mucous membranes & their secretions, intact skin and antimicrobial substance like fever, inflammation, phagocytes like macrophages, dendritic cells as shown in figure 3. When any pathogen (bacteria, viruses, protozoa) exposed to the body then it comes across 1st line of defense being resisted by intact skin, secretions of mucous membranes and food and environment competition with normal inhabiting microorganisms inside the body. However, after breaching 1st line of defense, there is 2nd barrier of phagocytes including neutrophils, macrophages, dendritic cells etc. to combat the infection along with inflammatory responses to recruit more phagocytes at the infection site (11). There is increased body temperature and release of antimicrobial substances to stop microbial multiplication. All is the function of innate immune system which functions non-specifically. Corona viruses multiply and induce illness as the body immune system takes time to recognize the antigen for the first time, to stimulate B cells for antibody production and to T cells for the induction of cell mediated immune response. So, in these circumstances coronaviruses successfully do the illness after entry.

Evasion of Coronavirus from innate immunity

There is manipulation in interferon (IFN) pathways by Coronaviruses. In a study it is observed by interference of coronaviruses with pattern recognition receptors (PRR) by interfering Toll-like receptors (TLRs) and retinoic acid inducible gene 1 (RIG-1) like receptors inducing high cytokine storm and non-productive inflammatory responses damaging the host cells and preventing anti-viral induction of interferon (12). It is evident that some structural and non-structural proteins also take part in inducing this response. Due to high production of these pro-inflammatory cytokines, there is influx of myeloid and neutrophil cells towards lungs inducing strong local inflammatory response that plays a very critical role in COVID-19 pathogenesis

There is initiation of innate immunity after the recognition of pathogen associated molecular patterns (PAMPs) by PRRs which trigger signaling pathways including nuclear factor kappa light chain enhancer of activated B cells (NF-kB), Interferon regulatory factor 3 (IRF3) and Activator protein 1 (AP-1) inducing huge production of type 1 interferon (IFN-1) which act via interferon α/β receptor (IFNAR) to activate interferon stimulated genes (ISGs) which prevent viral entry and replication inside the cells thus acting as innate antiviral defense (13). SARS-CoV-2 has the ability to manipulate this key antiviral defense by antagonizing IFN-1 production and by up regulation of ACE-2 which is considered as ISG and initiate early viral pathogenesis (14). A study conducted to demonstrated the role of INF-α in preventing *in vitro* replication of SARS-CoV-2 but it is still not clear that INF therapies would be better to prevent *in vivo* viral replication in COVID-19 patients, however, in a study conducted we found the more severe clinical outcomes of COVID-19 patients whose failure in INF-α production observed the modest beneficial effect of INF-α given to COVID-19 patients in combination with other drugs like lopinavir, ritonavir and ribavirin. Coronaviruses manipulate and interfere with the IFN production due to their structural (M and N proteins) and non-structural proteins (NSPs) by adopting strategies like avoidance from PRRs recognition and by suppressing IFN production and signaling pathways. Coronaviruses hide their RNA genome from PRRs (cytosolic & endosomal) detection as they multiply in double membrane vesicles and exclude themselves from these PRRs. The high rate of infection and death in COVID-19 is associated with pro-inflammatory cytokines including cytokine storm The actual detailed mechanism is still not known, but the studies being conducted on COVID-19 patients indicated high number of neutrophils and monocytes in the lungs along with other cytokines in serum such as IL-17, IL-10, IL-6, IL-2, TNFα, various chemokines and granulocyte colony-stimulating factor (G-CSF).

The production of pro-inflammatory cytokines is stimulated by some immune and non-immune cells and in a recent study found a large population of monocytes (CD163+, CD206+, CD68+, CD80+, CD14+, CD16+, CD11b+), IL-6+, IL-10+, and TNFα+ in peripheral blood of the COVID-19 patients who were admitted in hospital and required a long hospitalization as well as ICU admission as compare to those COVID-19 patients who did not require ICU hospitalization. But some authors claim that the size and pattern of marker expression on these cells indicate that these are the subsets of inflammatory dendritic cells (DCs) which should be further investigated (15). Recently, there was detection of two new chemokines: monocyte chemoattractant protein 1 (MCP1) and monocyte-chemotactic protein 3 (MCP3) in COVID-19 patients. These chemokines attract monocytes, T cells and dendritic cells at the site of inflammation (16).

Evasion of Coronaviruses from Pattern Recognition Receptors (PRRs)

Coronaviruses not only manipulate type 1 interferon and cytokines responses, but also avoid themselves from the recognition of PRRs such as retinoic acid-inducible gene 1 (RIG-1), toll like receptors 3 (TLR3), TLR7, and they suppress PRR and toll like receptors (TLRs) signaling (17). CoVs replicate inside the double membrane structures of endoplasmic reticulum (ER) because ER does not have PRRs (18).

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