ImmunobiologyOf N-Cov Spike Protein

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Abstract:Immunobiology is the branch of science that deals with immunological effects which includes phenomenan like infectious diseases, growth and development, hypersensitivity, heredity, aging and transplantation. In this review article, we have compiled the immunobiology of the nCoV, which has led to the world wide panic causing a major pandemic. Coronavirus (CoV) is a large family of viruses that has led to mild to severe illness, with magnified cytokine storms in the lungs. The severe forms of these viruses involve Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). A new strain of virus that had not been earlier detected in humans is the Novel coronavirus (nCoV). The major structural protein, the spike protein S seems to be the highly potent moiety involved with viral fusion and entry into the host cells through ACE receptors. This review thus throws insights into the immuno-biology of the spike protein and its role in the immuno-pathogenesis of CoV.

Keywords :
Immunobiology, Immunology, nCoV, Novel coronavirus, Spike protein

1. INTRODUCTION:

The world wide pandemic COVID-19 emerged from Wuhan city, located in the Hubei province in China (Wang, Tang, and Wei 2020). Numerous cases of pneumonia due to unknown etiological factors were reported, in the said place from December 8, 2019 and henceforth. Later the World Health Organization named a group of viruses as Novel coronavirus or nCoV- 2019 (Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention 2020). This Novel coronavirus was isolated from the throat swab of an infected patient, who had been infected in this infectious pathogen and had shown respiratory system disturbances. Later on the Coronavirus study group renamed 2019-nCoV to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Burki 2020).

This pathogen nCoV is highly contagious and has a high incubation period. The evolutionary process of this pathogen is directly involved with the oral cavity. Beta cyclodextrins are an excellent choice to be used in mouth rinses which will contribute to reduce the viral load and accomplish fight against their transmission (Shahana and Muralidharan 2016). Chlorhexidine mouthwashes can also be used as they facilitate viral lipid membrane disruption (Renuka and Muralidharan 2017). Due to causes like imbalance in renin angiotensin mechanism and hyoxemia, cardiovascular diseases are induced by nCoV(Paramasivam, VijayashreePriyadharsini, and Raghunandhakumar 2020). The Spike protein is a large type 1 transmembrane protein which has a range of 1160 amino acids for avian Infectious Bronchitis Virus (IBV) and around 1400 amino acids for Feline Coronavirus. The glycosylated spike protein resembles a crown like appearance. The spike proteins arrange themselves into trimmers on the surface of the virion, leading to the distinctive Corona or crown shaped appearance (Kundu and Bhowmikn.d.). The ectodomain of every CoV spike proteins share the same Organization in their domains : a N-terminal domain named S1 that is accountable for receptor binding action and a C terminal S2 domain which is accountable for fusion.

Previous research studies have reported the use of glycosylated spike protein for the entry of the virus into the host cell by fusion mechanism. In an article by Shereen MA, et.al, it is stated that spike protein is a trimeric class one fusion protein which exists in a metadata level perfusion (Shereen et al. 2020). It also undergoes a substantial structural rearrangement to accomplish the fusion action of the membrane of the virus with the cell membrane of the host. In an article by Li X, Geng M, et.al, it is said that novel coronavirus is a variant of coronavirus derived from an animal source (Li et al. 2020). It is then transmitted from the animal host to humans later. The significant challenge faced with these viruses is their evolutionary nature. In association with nCoV, other respiratory viruses like Acinetobacterbaumannii are also seen in affected patients (Girija AS and Priyadharsini J 2019),(Priyadharsini et al. 2018b). This is because microbes like A.baumannii and A. flavus are used to drug resistance (Girija, Shoba, and Priyadharsini 2020). To overcome the superinfection caused by this virus, anti MRSA empiric treatment could also be considered (Ashwin and Muralidharan 2015). Phytochemicals derived from Laurasnobilis are effective against inflammation as they inhibit SARS-CoV-2 protease (M, Geetha, and Thangavelu 2019). An intimate understanding on the immunobiology of nCoV spike protein is necessary to design, evaluate and synthesize novel drugs and vaccines against n-CoV. Sulfamethoxazole in combination with Trimetropin can be used for revival of renal function in patients affected by this pathogen (Girija, VijayashreePriyadharsini, and Paramasivam 2019). The review is thus an overview on the spike protein and its immunology behind inducing the covid disease by n-CoV.

2. RETRIEVAL OF LITERATURE DATA :

Various research articles were searched from different search engines like MeSH, PubMed, core, Google Scholar, Cochrane and so on. Data collection was made and information was retrieved by searching the keywords nCoV, Novel coronavirus, immunobiology, spike protein and glycosylated protein. A total of around 40 articles were reviewed thoroughly to write this review. The time period of the articles reviewed ranges from 2010 to 2020. The inclusion criteria for the article searched include articles related to immunobiology, spike protein and novel coronavirus. Exclusion criteria taken into consideration are articles highlighting the general information on covid. All these data were reviewed properly and analysed to conclude about the immunobiology of spike protein of nCoV.

Spike protein - The route of viral entry :

The entry of the virus into the host cell membrane relies on the interplay between the virion and the host cell. The glycosylated spike protein mediates the entry of these pathogens into the host cell (Hemmati et al. 2020). The spike protein present in the virus binds to its receptor human ACE2 through its receptor binding domain. The cells with ACE2 expression may act as target cells and are susceptible to nCoV infection. Such cells are type 2 alveolar cells of the lungs and bladder urothelial cells (Girija, Priyadharsini, and Paramasivam 2019). It is activated then proteolytically by human proteases (Kawasaki and Adachi n.d.). The cell entry of the virus is pre activated by proproteinconvertase firings, reducing its dependence on target cell protease for entry (Tuncer, Dogan, and Ozyurt 2020). The high human ACE2 binding ability of the Receptor Binding Domain (RBD), preactivation of the spike by furin and the presence of hidden Receptor Binding Domain in the spike easily allows the virus to achieve efficient entry into host cell, evading all the immune surveillance.

In other words, after the initial binding of the receptor in the enveloped virus, they need to fuse their envelopes with the host cell membrane to deliver their nucleocapsid to the respective target cell. The spike protein plays a dual role in the entry of the host cell. It is by mediating receptor bindings and membrane fusion. Proproteinconvertases are present which is a family of serine secreting protease which acts as regulator for many different biological processes and actions. The spike protein of the novel coronavirus seems to have a furin like site of cleavage (Choudhury 2020).

Fusion mechanism of n-CoV :

The novel coronavirus has two domains: N terminal domain which is named as S1. This S1 domain is responsible for the binding of the receptor. The other domain is the one responsible for fusion. The novel coronavirus spike protein is a class 1 fusion protein that can lead to viral entry and cytokine storm (Girija, Shankar, and Larsson n.d.). The characterisation feature of this class of fusion protein is the formation of alpha helical coil structure. The S2 subunit is the most conserved region of the protein unlike the S1 protein (Lu et al. 2020).

Both the sub domains in S1 are able to function as Receptor Binding Domain and they bind a variety of proteins and sugar based moieties (Table 1). The 2019 nCoV has S-HR1 and S-HR2 (heptad repeat) playing key roles in mediating fusion and entry into the host cell . As the S2 subunit is used for the fusion of membranes, it is considered very significant. The conformational changes that seem to occur in the S2 subunit may be caused or triggered by the interaction between Homologous receptors present and S1 subunit (Paudeln.d.).

This conformational changes caused due to the specific interaction between S1 subunit and the homologous receptor results in fusing action between the virus envelope and membrane of the cells (Rota et al. 2003). It also causes the release of nucleocapsid into the cytoplasm. This process is triggered when S1 subunit happens to bind with the host cell receptor. As the receptor binding gets unstabilised, shedding of S1 subunit occurs leading to post fusion conformation (Premanandh and Salem).

Fusion Inhibitors and their role:

Several mutated amino acid residues present in the HR1 domain may be associated with the enhanced interactions seen with the HR2 domain. FK1, which targets the HR1 domain, could

be able to inhibit the infection by doing tests in divergent human coronavirus including SARS-CoV and MERS-CoV(Pratha and Geetha 2017). The most patient fusion inhibitor is EKIC4 which acts against SARS-CoV-2 glycosylated spike protein mediated membrane fusion and pseudo virus infection with IC 50S of 1.3 and 15.8 nM. About 241 and 149 are capable of folding with more potent than that of EK1 respectively.

Novel point mutations in 2019- nCoV S2 subunit my change interaction pattern between HR1 and HR2 domains in the post fusion core and affect the 6-H formation. In 2019 nCoV HR1 and HR2 regions will be able to interact with each other and form6 HB and it suggests nCoV HR2P may inhibit novel coronavirus fusion and entry into the target cell (Tian et al. 2020). Hesperidin which is present in citrus fruits like orange peel can be used for the prevention of COVID 19 as it targets the three main receptors RBD-S, PD-ACE2 and SARS-CoV-2 protease (Vaishali and Geetha 2018). Defensins are a group of amphiphilic AMPs (Antimicrobial peptides). Human Defensin which is efficiently active against Multidrug-Resistant AcinetobacterBaumannii is also effective against nCoV in renal cells (Priyadharsini et al. 2018a), (Smiline, Vijayashree, and Paramasivam 2018).

Immune cross-reactivity with SARS-CoV:

Considering the relatively high identity found between the receptor binding domain (RBD) in 2019-nCoV and SARS-CoV, it is of utmost urgent to assess the cross reactivity and anti SARS-CoV antibodies with 2019-nCoV spike protein (Tian et al. 2020). It is also significant for important implications in rapid development of vaccines and therapeutic antibodies against 2019 Novel coronavirus. Some of the potent antibodies like SARS-CoV specific neutralising antibodies like m396, CR 3014 which targets the human ACE2 binding site in SARS-CoV which failed to bind to 2019-nCoV spike protein. The difference in the RBD of SARS-CoV and 2019-nCoV has a critical impact for the cross reactivity of neutralising antibodies (Wang et al. 2020).

By some genetic analysis, it was found that SARS-CoV was in close relation with group 2 virus. Antigenic cross reactivity was established between SARS-CoV and another known coronavirus with group 1 coronavirus as an exception. Moderate two way cross reactivity was observed between SARS-CoV and porcine CoV while weaker cross reactivity in feline and canine CoVs. By finding the cross reactive and non cross reactive regions, specific antibody assays will be developed which will help in easier screening and diagnosis.

When seen in comparison to SARS-CoV, 2019- nCoV seems to be more readily spreading from one person to the other leading to the declaration of Public Health Emergency of International Concern by the World Health Organization. As reported by BLAST analysis, the identity of sequence of ORF1ab protein among 2019-nCoV and SARS-CoV is above 90% with the query cover of about 100% thereby proving that 2019-nCoV and SARS-CoV share a good sequence homology (Chen and Qiu 2020). It is also seen that SARS glycosylated spike protein can be used as a good template for building 2019-nCoV surface glycoproteins. The identified homologous of SARS spike protein and 2019-nCoV is seen to be 34% with the rate of query average as 74% (Xia et al. 2020a).

Immunogenicity of the spike n-CoV

The receptor binding domain of the spike protein of Pangolin CoV which is virtually identical to the 2019-nCoV with the only difference being one amino acid difference. External sub domain in 2019 n-CoV shares only 40% amino acid identity along with other SARS related

coronavirus. The S1 subunit of the nCoV contains a single peptide N terminal domain (NTD) receptor binding domain (Xia et al. 2020b). The S2 subunit contains conserved fusion peptide (FP) and HR1, HR2 along with cytoplasmic domain. Most of the amino acid differences in RBD are located in external subdomains that are responsible for the direct interaction with the host receptor.

A small envelope protein called E protein is present in nCoV along with the spike surface glycoproteins (S protein), the matrix protein (M protein), nucleocapsid protein (N protein) and other non structural accessory proteins (Chen and Qiu 2020). E protein is a small transmembrane protein that appears on the envelope. The coronavirus has a diameter of about 80 to 120 nm. The club-like appearance providing S protein has membrane glycoproteins or M protein in association on the envelope. The n protein or nucleocapsid protein will attach itself to the RNA genome in the form of beads leading to the formation of helical and symmetrical nucleocapsid(Kumar n.d.). Intravenous immunoglobulin therapy can be considered for reducing inflammation and eliminating opportunistic pathogens like Enterococcus faecalis(Marickar, Geetha, and Neelakantan 2014).

3. CONCLUSION:

Spike protein of n-CoV plays a vital role in n-CoV viral entry and fusion in the host cells. An intimate understanding of the structural, chemical and immunological parameters on the spike protein would pave the way to the design and evaluation of novel drugs and vaccines against n-CoV. A knowledge on the post translational modifications and mutations in the strains might also influence the biology of the spike protein and thus can cause variations in the covid pathogenesis too. This review had thus thrown insights into the immuno-biology of the spike protein of n-CoV leading to the better understanding on the immuno-pathogenisis of the covid disease.

AUTHOR CONTRIBUTIONS :

M.Rithanya contributed to the execution of the work, data collection and drafting of the manuscript. Dr. Smile Girija AS contributed to the concept, design of the study, validation of the data collection, revision and proofreading of the review.Dr.Brundha MP contributed to the validation of the data collection, revision and proofreading of the review.

CONFLICT OF INTEREST :

None to declare

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VIRUS GENUS	**VIRUS SPECIES**	**RECEPTOR FOR N-TERMINAL RBD**	**RECEPTOR FOR C-TERMINAL RBD**
Alpha coronavirus	TGEV	sugars	APN
Alpha coronavirus	PRCoV	-	APN
Alpha coronavirus	HCoV-229E	-	APN
Alpha coronavirus	HCoV-NL63	-	ACE2
Beta coronavirus	SARS-CoV	-	ACE2
Beta coronavirus	MHV	CEACAM1	-
Beta coronavirus	HCoV-OC43	sugars	-
Beta coronavirus	BCoV	sugars	-

Table 1: Various corona virus and their receptors for fusion mechanism