AN OVERVIEW ON PROTEINS INVOLVED IN SARS-COV-2

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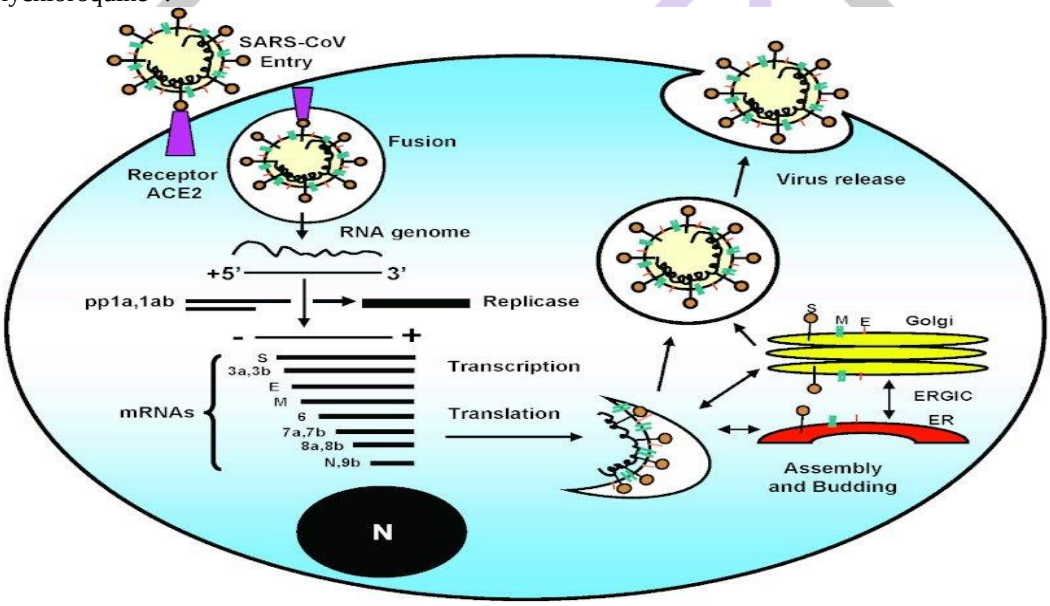
***Abstract*: COVID-19, SARS-COV-2 has become a global pandemic, where it belongs to the member of Beta corona virus. The infection of covid-19 has been so rapid, due to its replication process; it involves the multiple organ damage. Most affected organ is the lung, where it binds to serine protease that is expressed in respiratory epithelial cells and results in the process of inflammation, by releasing the inflammatorymediators such as cytokines, tumor necrosis factor. The proteins involved in SARSCOV-2 are responsible for the pathogenesis and its replication process. These proteins include 4 structural proteins S, M, N, Eproteins, accessoryproteins (ORF1a, 1b…) and 16 non-structural proteins (Nsp1-Nsp16).**

***Keywords*: SARSC0V-2, structural proteins, non-structural proteins**.

Introduction:
SARS-COV2 enters into the host cell, by utilizing its structural proteins and continues its replication process by use of its other proteins I; e nonstructural and accessory proteins. The cycle includes the steps such as attachment, entry, replication, biosynthesis and release. The entry of virus may occur via, endosomalentry, in which the virus after binding to ACE-2 forms an ACE-2 -virus complex, which enters into host cell endosomes via endocytosis, where the complex gets cleaved by endosomal cysteine protease cathepsinB and is further released into cytoplasm. The drugs that inhibit this protease enzyme are called lysosomotropic agents, for example Hydroxychloroquine [1].



Virus consist of 4 structural proteins i;e Spike protein, Membrane protein, Nucleocapsid-protein and Envelop protein [2] and includes16nonstructuralproteins(nsp1,nsp2,nsp,3,nsp4,nsp5,nsp6,nsp7,nsp8,nsp9,nsp10,nsp11,nsp12,nsp13,nsp14,nsp15,nsp1).

Structural proteins:
S-Protein:
S-protein, is a crown like glycol-protein, which is further cleaved into S1 (head) and S2 (stalk). These two subunits contain receptor binding domain (RBD)that plays an important role attachment of virus to host. This RBD binds to ACE-2 , which further results in activation of Furin thereby cleaves the S protein providing the access to virus for the entry.[2],[3] Usually ACE-2 acts as a protector of vascular tissue ,by maintaining blood pressure and balancing the angiotensin effects .In case of person with SARS COV-2,there is either depletion or decrease in the ACE-2 is observed, due to which there can be lung damage or loss of smell .The lung damage is most common with patient associated with diabetes in COVID-19 patient, as the expression of ACE-2 is decreased after the RBD binds to serine protease [15] expressed in lungs, this further stimulates the Furin activation resulting the cleavage of spike protein [14] and facilitates its entry into the host cell.

M-Protein:
It is responsible for maintaining the shape [4] of viral envelope and consist of 2 domains called Amino terminus, longcarboxy terminus [2,5]. One of the most important step in replication i;e viral assembly is carried out by M-protein, by binding itself to N-nucleocapsid protein and exhibits the encapsulation of RNA genome.

N-Protein:
This protein are considered as the abundant proteins present in the SARS-COV-2 that provides stability by binding to the viral RNA, thus forms helical ribonucleocapsid complex by interacting [10] with positive strand of RNA strand of viral genome, exhibiting its role in transcription and translation. It consists of 2 domains, N1b and N2b [9].It extends its role in M-M protein interaction, required for assembly of virus and its replication.

E-protein:
It is the smallest of the structural protein and is involved in all most all the steps of viral replication and results in pathogenesis. It has an ability to create an ion channel [6, 8], although it is a small integral protein. It has 3 domains such as short hydrophilic amino terminal, long hydrophobic transmembrane domain, C-terminal.

Non-structural proteins:
Apart from structural proteins, the virus also consists of some accessory proteins that help in synthesizing the nonstructural proteins. The RNA genome of covid virus consists of3 'polyadenylated end that is responsible for synthesis of structural proteins.and 5´cappedend codes for accessory proteins that includeORF1a, ORF1b, ORF3a,OR6,ORF7a,ORF7b, ORF8,ORF9b,ORF9c,ORF10,etc where ORF represents open reading frames. The ORF1a and ORF 1b, has a main role in SARSCOV-2, since they are translated to PP1aand PP1ab(polyproteins), further gets processed by viral proteins i;e(papain and main protease),eventually resulting in the synthesis of nonstructural proteins. The nonstructural proteins conjugates with the host factors to form a replication transcription complex inside the vesicles, this RTC acts as amin hub for viral transcription and therefore NSPs are otherwise termed as RNA-dependent polymerase. The drug Remedesivir acts by inhibiting this enzyme.

Nsp1:
This binds to 40s ribosome and interferes with host cell protein synthesis by degrading host m-RNA and cleaving the endonucleotide, further allowing translation via, certain unknown mechanism.

Nsp2:
The two proteins of host such as Prohibitin 1 and prohibitin2 (PHB2)[7] play an important role in cell cycle progression, cell differentiation and thus maintain its cell cycle. This Nsp2 binds to these proteins and thereby disrupts the host cell environment.

Nsp3:
It is considers as the largest protein also called papain like protease [6] that are present on the cytoplasmic surfaces, responsible for forming RTC, a complex required for transcription and replication of the virus. It consists of various domains such as N-terminal Nsp3a domain, -X, SARS uniquedomainer domain and others. Macrodomain is involved in replication by decrease the ADP ribosylation that results in alteration the DNA repair mechanism.
Nsp4: It contains transmembrane 2 and interacts with Nsp3 and extends its role in membrane rearrangement responsible for viral replication [6, 11]. Nsp5 which is called 3C like proteinase, upon cleavage forms a mature and intermediate nonstructural protein[12]
Nsp6: is responsible for assembly of replicase proteins by generating autophagosomes, thus involves in replication. Nsp7 is responsible for RNA polymerase activity [13] by interacting with the Nsp8and 12, which are considers as the peptide factors.
Nsp9: exhibits a tetrameric structure and it has a capacity to bind to nucleic acids in the protein, due to its dimerization [17]property. Nsp10 stimulates the activities of EXON -N-terminal 3-5'exonuclease activity, domain of Nsp14 along with 2-OMTASE activity I; e Methyltransferase activity of Nsp16 and plays a role in RNA replication, throughthe interaction with these proteins.[16]
Nsp12: proteins forms large multi protein complex called RNA dependent polymerase [17], by interacting with Nsp7and Nsp8 proteins. Nsp13 has its interactions with Nsp8 and 12, where it shows its replicase activity. Most of the anti-viral drugs considers this Nsp13 as targets.
Nsp14: consist of 4 structural regions i;e Nsp10 binding site, EXON domain ,C terminal N7 MTase domain and flexible hinge region. It includes EXON activity and methyltransferase activity [18] due to its proof-reading activity, thereby involving in replication mechanism of the viral.
Nsp15: it cleaves the RNA at specific site i;e at 3´end of uridylates ,thereby called endoribonuclease.it assembles itself as compact hexamer that is required for its activity.it includes 3 domains such as small-terminal domain, middle domain ,C-terminal catalytic. An FDA approved drug Tipracil acts by inhibiting the Nsp15 activity.
Nsp16: This protein cannot act individually [19] and needs to be interacted with Nsp10, where the Nsp10 protein binds with Nsp16 via hydrophobicbond. on the other hand, it acts as one of the targets for drugs used in COVID-19.

Conclusion
As a bottom of the line, both the structural and Non-structural proteins have their vital role in the access to virus entry and replication inside a host cell. Apart from their role in pathogenesis, they are considered as the best targets for some antiviral drugs.

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