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Commentary

Mechanism of infection of SARS-CoV-2 and gender based differential impacts

Suvendu Ghosh[1], **Partha Sarathi Singha**[2], **Debosree Ghosh**[3]*

[1]*Dept. of Physiology, Hooghly Mohsin College, Hooghly, West Bengal, India*
[2]*Dept. of Chemistry, Government General Degree College, Kharagpur II, West Bengal, India*
[3]*Dept. of Physiology, Government General Degree College, Kharagpur II, West Bengal, India*

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ABSTRACT

The world has witnessed a pandemic in the recent past. COVID-19 has been a nightmare for all. The virus SARS-CoV-2 causes the disease. The impact of the pandemic on human life and on various aspects of the society is still prevailing. No specific effective drug has yet been formulated to completely combat the virus. It took more than a year for the researchers and scientists around the globe to understand the mechanism of the virus infection. For the time being vaccines have been designed and those seems to be effective in preventing the infection to some extent. The pattern of infection by SARS-CoV-2, symptoms, pathophysiology, complications and fatality associated with COVID-19 has been found to be dependent on various factors and varies from person to person. The virus has been found to have differential mechanism of infection and impacts in male and female. The X-Chromosome plays an interesting role.

As per the repertories of the genomic constitution and their phylogenetic relationships of coronaviruses, the virus have been classified into the subfamily Coronavirinae. This consists of four genera i.e., Alpha Coronavirus (αCoV), Beta Coronavirus (βCoV), Gamma Coronavirus (γCoV), and Delta Coronavirus (δCoV).[1] The size of this virion ranges from 70 to 90 nm.[2] Although, pleomorphic, it's normally spherical in shape, comprising a capsid of matrix protein containing a single sense positive strand RNA and nucleoprotein.[3] Unlike other RNA virus, SARS-CoV-2 has a bigger genome size (26 to 32 kb) and consists of 6-11 open reading frames (ORFs) encoding 9680 amino acid polyproteins.[4] The first ORFs (1a and 1b) constitutes about 67% of the entire genome.[4,5] Both the ORFs have a frameshift in between and codes for two polypeptides pp1 and pp1a which are modified by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro) and one or two papain like proteases into 16 nonstructural proteins.[6] The non structural proteins (Nsps) include two viral cysteine proteases including papain-like protease (nsp3), chymotrypsin-like, 3C-like, or main protease (nsp5), RNA-dependent RNA polymerase (nsp12), helicase (nsp13), and others expected to be involved in the transcription and replication of SARS-CoV-2.[7] All the structural and accessory proteins are translated from the remaining ORFs of the viral genome. Four major structural proteins encoded by ORFs 10, 11 on the one-third of the genome near the 3′-terminus are spike surface glycoprotein (S), membrane (M), nucleocapsid protein (N), envelope (E) and accessory proteins. N-terminal glycosylated ectodomain is present at the N-terminal end of M protein that comprises of three transmembrane domains and a long C-terminal domain inside the virion.[8] In addition, the SARS-CoV-2 encodes special proteins 3a and

* *Corresponding author*.
E-mail address: ghoshdebosree@gmail.com (D. Ghosh).

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3b. All these proteins are involved in viral replication, infection and life cycle. The M and E proteins are required for virus morphogenesis, assembly, and budding, S glycoprotein (fusion viral protein) comprises of two subunits S1 and S2. The S1 subunit has a signal peptide, N-terminal domain (NTD), and receptor-binding domain (RBD). The S2 subunit has two seven repeat regions known as HR-N and HR-C, which form the coiled-coil structures surrounded by the protein ectodomain. The S protein contains a furin like cleavage site (PRRARS'V) between S1 and S2 subunits that is processed during the biogenesis. The S glycoprotein is primarily responsible for interaction of spike with the ACE2.[9]

Specifically, this virus affects the local components of the renin–angiotensin system (RAS) viz. ACE, ACE2, AT1R, AT2R, MAS and the protease. TMPRSS2-(which is necessary for virus entry) may also get affected just as in case of other SARS- CoV virus. Prior to attachment to its cytosolic receptor (ACE2), by the spike glycoprotein, priming of an enzyme serine protease TMPRSS2 is essential for viral envelop fusion and internalization of virus genome (SSRNA) into the host cell by endosomal pathway.[9] This event is followed by transcription and translation of the genome in a synchrony of continuous and discontinuous RNA synthesis of genomic and sub genomic RNA mediated by a replication-transcription complex and the involvement of replicate protein as well which is encoded by a replicase gene. This mechanism of viral genomic multiplication coding leads to the synthesis of the appropriate viral proteins. Unlike other viral RNA processing, enzymes that are relevant for synthesis of required viral proteins are specific endoribonuclease, 3′-to-5′ exoribonuclease, 2′-O-ribose methyltransferase, ADP ribose 1′-phosphatase and cyclic phosphodiesterase 8 (13, 14). Next, assemblage of virion takes place by the association of viral RNA and protein in endoplasmic reticulum (ER) and Golgi complex. Finally, the newly formed virions are subsequently released out of the cells via vesicles by budding from the internal cell membrane.[10]

The N protein of this SARS-CoV-2 activates the AP1 pathway and certain cellular transcription factors resulting in selective alteration of some specific cellular pathways. SARS-CoV-2 proteins Orf3b, Orf6, and N proteins are also liable to inhibit interferon action and expression of IFN-β and IRF-3 by diverse mechanisms.[11] The virus affects both innate and adaptive immune responses and specifically affects the respiratory system by the generation of commonly known "cytokine storm".

Upon entry in the respiratory epithelial cells, the virus initiates proinflammatory immune responses that are facilitated by NF kappa B p65 and p 38MAPK T helper cells 1 and CD14+ and CD 16+ monocytes.[12] This further stimulate granulocyte macrophage colony stimulatory factor with the secretion of huge amount of IL-6 and TNF-alpha, triggering disseminated intravascular coagulation (DIC), intravascular permeability, plasma leakage and respiratory distress syndrome and accessory cardiorespiratory failure and death in many individuals.[13] The role of innate immune cells specifically the neutrophils are also not to be overruled in such infections, since neutrophils are the first line of the immune responses that produces IL-8 that indulges other neutrophils to form Neutrophil extracellular Traps (NET).[14] NET further increases the secretion of IL-8, dendritic cells and macrophages activated by other viral derivatives activating Mϕ and dendritic cells producing the above mentioned proinflammatory mediators and cytokines responsible for generation of the cytokine storm (IL-1, IL6, IL-8), TNFα, monocyte chemoattractant protein-1(MCP) and IP-10 that have the trend for respiratory epithelial infection. In addition, the dendritic cells mediate adaptive immune responses by presenting viral products via MHC receptors and activates T cell population to differentiate in TH1 and TH2 subsets under the influence of IL-12 and IL-4 respectively. Further Th) cells are stimulated by the secreted interleukins – IL-6, TGF- β, Il-21 etc. to differentiate into TH-17. Th1 cells induce CD8 cells to secrete INF-γ to wash away the infected cells. In association, Th 2 stimulates B cells to produce plasma cells that produces antibodies for providing antibody mediated immune response. The available literature suggests that the virus is not just confined to the respiratory system but it is circulated to other body fluids like the saliva, tears, GI tract and even to the seminal fluid and testis as well by means of viral shedding.[14,15]

Li et al.,2020, reported that SARS-CoV-2 RNA has been found in the semen samples of six out of 38 patients who were in acute phase of the infection and also some were in recovery phase.[16] However, Pan et al., was unable to characterize this virus in the semen of 34 COVID-19 positive patients.[17] The difference might involve these three possibilities: ACE2 gene is located on the short arm of X chromosome (Xp22.2), TLR7 etc. In females one of these X chromosomes is randomly suppressed during X chromosome inactivation. However, the ACE2 gene escapes such inactivation leading to equal expression of this gene on both the two chromosomes. While considering the binding of the SARS-CoV-2, 16 receptor binding motif (RBF) of this virion are recognized by 16 ACE2 molecules out of 20 ACE2 residues by one X chromosome both in males and females. Unlike males, the chances of binding of ACE2 to RBM in the other X chromosome of the female is low thus sparing the ACE2 to perform its normal functions by the non-canonical pathway to produce Angiotensin I-VII (Ang I-VII) from Angiotensin II (Ang II). This may help the products to show their normal immune protective activity.[18,19] TLRs are well known for recognizing pathogen associated molecular pattern (PAMPs) of viruses to initiate innate immune responses. X chromosome expresses the various subsets of TLRS like 3, 4 and 7. Amongst these

TLR3&4 have TRIF domain engaged to provide defense against SARS-CoV-2. In addition, TLR4 signals via IL-1 receptor associated kinases (IRAKs) and IKKγ both of which are expressed in long arm of X chromosome (Xq28) in females to confer immunity against SAS-CoV2.[19]

Dendritic cells also take advantage of TLR7 encoded by the other X chromosome in females, acts as sensor of GU rich single stranded RNA and increases the expression of INF-γ.[20] Finally, this differential expression of X chromosome in both the sexes may provide an elevated TLR signaling, increased dendritic cell activation and decreased cytokine storm in females to defend SARS-CoV-2 infection unlike males with higher Ang II, reduced availability of Ang I-VII and lower titers of ACE2 manifesting the differences in rate of mortality and morbidity to SARS CoV-2 infection.[19]

The entire world including India has witnessed during the pandemic[21] a grave period of unknown consequences, lack of enough knowledge about the virus, helplessness, casualties and many more distresses. Fortunately on today's date, we have a clear picture of the molecular mechanism of the pathophysiology of COVID-19. We have the vaccines, some medicines and potent antiviral formulations against the SARS-CoV-2[22] have also been recognized against the deadly virus. With these we are hopeul to combat the pathogen successfully. A more extensive understanding of the differential impact of the disease, its mechanism and course of infection specifically in men and women may help us to address certain issues like infertility and other associated ailments with COVID-19 in a better way. This will also open up new ways to fight back the virus more effectively and precisely.

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Author biography

Suvendu Ghosh, Assistant Professor https://orcid.org/0009-0009-8384-5984

Partha Sarathi Singha, Associate Professor https://orcid.org/0000-0001-8255-3271

Debosree Ghosh, Assistant Professor https://orcid.org/0000-0002-4382-4283

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