Model of trigger mechanisms of SARS CoV-2 infections

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ABSTRACT

Coronavirus disease-2019, is a pandemic that is causing great loss of life and economy. Knowledge of the pathogenesis of the disease is required for the control and treatment of clinical manifestations. The aim of this review is to analyze the information on the molecular mechanisms that trigger the alterations caused by SARS-CoV-2 from published articles related to COVID-19. The onset of the COVID-19 virus infection in humans occurs when the SARS-CoV-2 S protein reaches cells containing ACE2 receptors, being mainly the upper respiratory tract, followed by the oral cavity, and in lesser frequency through the conjunctiva. Inflammation and thrombus formation in symptomatic patients have been the major cause of SARS-CoV-2 aggravation, this occurs largely due to the imbalance of regulation by diminishing ACE2 receptors, which serves to activate the regulatory axis Ang-II→ACE2→Ang-(1-7)→MAS receptor, which counteracts the negative actions caused by Ang-II. The ACE2 is also the main receiver for the SARS-CoV-2 so that it can trigger the virulence processes in the host.

Keywords: Coagulation, COVID-19, Pathogenesis, Pyroptosis

INTRODUCTION

In a city of 11 million people called Wuhan, Hubei Province, China, an increasing number of cases of pneumonia have been reported as of December 2019, with unknown etiology, and all were scattered and linked to the wholesale seafood market in Huanan (southern China).¹ On February 11, the World Health Organization announced a new name for coronavirus disease - 2019 (COVID-19).² The coronavirus of COVID-19 is a pathogen regulated by the spike glycoprotein (S) which allows it to be an attractive target for person-to-person transmission when the secretions emitted (droplets) by coughing, sneezing and sometimes by speech produced by infected people, reach the upper respiratory tract (nasal mucosa), mouth (tongue and oral and gingival mucosa) or eye mucosa. The onset of a COVID-19 infection in a person occurs when the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), comes into contact with the host cell to deliver the genetic material.³,⁴ After initial contact with the cell surface, the virus can penetrate the cell through endocytosis, phagocytosis or membrane fusion.⁴ Other recent studies, when testing stool and urine samples from patients diagnosed with COVID-19, have found SARS-CoV-2.

This expression is probably given by the predominance of ACE2 in the intestine and kidneys, infected by SARS-CoV-2 and can affect cells of these tissues to reach the feces and urine which would increase the possibility of transmission through the fecal / oral route and body fluids (urine).⁵ Here, we review the molecular mechanisms of COVID-19 disease, and the mechanisms by which patients affected with SARS-CoV-2 express symptomatology, based on the literature and experience.
DISCUSSION

The clinical manifestations caused by SARS-CoV-2 mainly include common symptoms such as: fever, dry cough and dyspnea mainly, followed by expectoration, muscle pain, headache, sore throat and others in less frequency the rhinorrhea, chest pain, diarrhea, nausea and vomiting. Background shows that SARS-CoV-2 has a higher preference for infecting the lower respiratory tract.6

SARS-CoV-2

SARS-CoV-2 is a human coronavirus related to SARS-CoV, belonging to the genus Betacoronavirus of the family Coronaviridae in the order Nidovirales. The coronavirus is composed of four major structural proteins: spike surface glycoprotein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N).7 The S-protein is a multifunctional type I glycoprotein that protrudes from the surface of the virus and can bind to the host cell. The entry of coronaviruses into host target cells requires the successful completion of two critical steps. The first is the binding of the coronavirus to the cell surface, to the host cell receptor. The second is the fusion of the viral envelope with the cell membranes, inducing particle endocytosis of virions, and then catalyzing the fusion between the host and the viral membranes, allowing the penetration of the virus genome into the cytoplasm, which enables viral replication.8

The S protein is also responsible for inducing host immune responses and neutralizing the virus by antibodies.9 These steps are controlled by the S envelope protein.10 In the case of SARS-CoV-2, the S protein shows a higher plasma membrane fusion capacity compared to SARS-CoV, with an affinity of 10-20 times, suggesting a high spread of the virus from human to human.11

The S protein is a class I trimeric fusion protein that exists in a metastable pre-fusion conformation showing substantial structural rearrangement to fuse the viral membrane with the host cell membrane. This process is triggered when the S1 subunit of the SARS-CoV-2 protein S interacts with the human angiotensin converting enzyme 2 (hACE2) cell receptor.12 The S protein comprises two functional subunits S1 and S2 that remain non-covalently associated (Figure 1). The individual S-protein monomers are assembled in trimers giving rise to masses that form characteristic spike structures around the virion.13,14 The SARS-CoV-2 domains S1 and S2 have two sequential cleavage sites R685/S686.15 The first cleavage event at the S1-S2 boundary probably facilitates the second cleavage event at the R797 position (S2' region) which is responsible for the fusion activation.16 The second cleavage occurs directly at the N-terminal end of the fusion peptide.13

Figure 1: A) Structure of the SARS-CoV-2 protein S. B) Schematic representation of the COVID-19 virus, M: Membrane glycoprotein; E: Envelope protein; S: Spike protein; N: Nucleocapsid protein.

The S1 subunit of SARS-CoV-2 is within the 14-685 N-terminal amino acids of the S protein, which contains the N-terminal domain (NDT), the receptor binding domain (RBD), and the receptor binding motif (RBM), which is directly involved in the peptidase domain (PD) binding of the host cell’s angiotensin converting enzyme 2.
After inserted hydrophobic functional amino acids, the SARS-CoV-S protein self-domain changes its conformation for increased accessibility to the host cell receptor. It is possible that the partial structure of the SARS-CoV-S protein contains a strictly hydrophobic element which could stabilize the fusion trimer and detachment of the S1 subunit for the approximation of the S2 subunit to the host receptor with stable post-fusion conformation. While the S2 subunit contains the main protein segments that facilitate virus-cell fusion, including the fusion peptide (FP), two heptad-repeat regions (HR1 and HR2), transmembrane domain (TM) and cytoplasmic domain (CP), which induce the set of mechanisms of fusion of the viral envelope with the cell membranes, making it the fundamental protein in the process of entry of the coronavirus.

The fusion peptide forms a short helix from which the strictly conserved hydrophobic residues are contained at an interface with other S2 elements. The FP is the functional fusion element of the S-protein, which is composed of a short segment of amino acids, mainly hydrophobic residues, such as glycine (G), that are inserted into the host cell membrane to trigger the fusion process.

After FP are HR1 and HR2 which are composed of repetitive heptapeptide with hydrophobic, hydrophilic, and charged residues. This allows the HR region to adopt a secondary alpha helix structure with a hydrophobic interface to drive membrane fusion. These S-protein changes are necessary to result in the formation of the helix array, post-fusion and fusion of the virus cells, which will allow close apposition and subsequent fusion of the virus and host lipid bilayers.

**Mechanisms of cell fusion and expression**

The SARS-CoV-2 drives receptor bonding and membrane fusion. However, to catalyze the membrane fusion reaction, the S-protein needs to be activated by an appropriate protease that lies between the S1 and S2 subunits (S1/S2 cleavage site), while the other S2' cleavage site lies after FP between the 812 and 813 amino acids, which allows fusion of viral and cellular membranes.

The existence of proteases in the plasma membrane pathway allows the virus to fuse through an early pathway in the plasma membrane, otherwise, the virus can fuse through a late pathway in the endosomal membrane being this the less frequent pathway.

The SARS-CoV-2 S protein makes use of ACE2 which is the main pathway of the angiotensin-renin system (ARS). SAR is an endocrine system whose physiological functions are electrolyte homeostasis, regulation of body fluid volume and cardiovascular control in the peripheral circulation.

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Figure 2: Schematic representation of a model of trigger mechanisms controlling molecular reactions in cells under normal and SARS-CoV-2 infected conditions. Ang-I: angiotensin I; Ang-II: angiotensin II; Ang-(1-7): angiotensin-(1-7); ACE: angiotensin converting enzyme; ACE2: angiotensin converting enzyme 2; AT1: Ang-II receptor type 1; AT2: Ang-II receptor type 2; MAS: Ang-(1-7) receptor; NO: nitric oxide; PGI2: prostacyclin; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; PI3-K: phosphatidylinositol 3-kinase; AKT: protein kinase B; NOS3: nitriccy oxide synthetase 3.
Renin is released from the juxtaglomerular cells of the kidney and acts on angiotensinogen (AGT), a precursor of macroglobulin, in an inactive angiotensin-I (Ang-I) decapeptide. However, inappropriate activation of this system results in abnormal sodium retention, potassium loss and increased blood pressure.\textsuperscript{22} For the classification of SAR, we divided into two pathways for the behavior of SARS-CoV-2 infections, being these the classical and non-classical pathway. The classical pathway consists of Ang-I, angiotensin converting enzyme (ACE), Angiotensin-II (Ang-II) and Ang-II receptor type 1 (AT1). The non-classical pathway is composed of ACE, Ang-II, ACE2, Angiotensin-(1-7) (Ang-(1-7) and MAS receptor (Figure 2).

ACE is the second enzyme in the Ang-II synthesis cascade, attached to the plasma membrane of various cell types, including the luminal surface of the vascular endothelium, are also present in the extracellular space, whose main physiological function is the conversion of the inactive decapptide Ang-I into the active octapeptide hormone Ang, which also degrades bradykinin into inactive metabolites, reducing serum levels of endogenous vasodilators.\textsuperscript{23,24} The human angiotensin 2 converting enzyme (ACE2) is a type I integral membrane protein that contains an N-terminal signal sequence of 17 amino acids and a hydrophobic transmembrane sequence of 22 amino acids near the C-end, followed by a cytoplasmic domain of 43 amino acids, which contains potential phosphorylation sites.\textsuperscript{25} The expression of ACE2 is involved in several organs of the human body mainly in the lungs, heart, kidneys, intestine, oral mucosa, nose, nasopharynx, stomach, skin, lymph nodes, thymus, bone marrow, spleen, liver and brain.\textsuperscript{26} Where the greatest predominance of ACE2 is found in pulmonary alveolar epithelial cells and enterocytes of the small intestine, however, the mucosa of the oral cavity has also been shown to contain high amounts of ACE2 and is higher on the tongue than on the oral and gingival mucosa, in addition to arterial and venous endothelial cells and arterial smooth muscle cells.\textsuperscript{2,27} Thus, the high content of ACE2 in lung epithelium, oral cavity and small intestine could be considered as the main entry routes for SARS-CoV-2 and would be a high potential risk to trigger infectious processes.

ACE2 has the function of hydrolyzing through its amino end, Ang-II into Ang-(1-7) vasoactive peptide with opposite properties to Ang-II.\textsuperscript{28} ACE2 also serves as a receptor for SARS-CoV-2. ACE2 not only facilitates virus invasion with SARS-induced infection and pathology through its cell receptor function for the virus. As a result of decreased ACE2 levels on the host cell surface, reduced ACE2 function leads to SAR dysfunction and increased inflammation and vascular permeability, this leads to acute effects on increased local levels of Ang-II, which likely contributes to acute lung injury and fibrosis caused by SARS.\textsuperscript{29,31} Ang-II is an octapeptide produced from angiotensinogen through enzymatic excision by renin and ACE, it is the main component of SAR that is cleaved by ACE2 that forms Ang-(1-7), whose function is the regulation of blood pressure, hydroelectrolyte balance, sympathetic nerve activity, cell proliferation, differentiation, regeneration, apoptosis and modulates inflammation.\textsuperscript{32} The main actions of Ang-II are mediated by two subtypes of G-protein coupled angiotensin receptors, having as receptor AT1 and the Ang-II type 2 receptor (AT2), which are seven-membrane glycoproteins with only 32-34% sequence homology.\textsuperscript{29}

Ang-II acts on AT1 receptors, is a strong activator of oxidative and inflammatory cascades, being involved in pulmonary disorders such as pulmonary arterial hypertension, pulmonary fibrosis, chronic obstructive pulmonary disease and acute respiratory distress syndrome and pyroptosis.\textsuperscript{33-38} However, AT2 receptors are widely expressed during fetal development, and their expression is restricted in adults, concentrating in a few organs such as the brain, adrenal glands, heart, kidney, skin in pathological conditions, fibroblasts.\textsuperscript{36} AT2 is usually induced by activation of Ang-II, through Ang-(1-7) and antagonizing effects mediated by AT1.\textsuperscript{37} The AT2 receptor has the function of neutralizing the over-stimulation of AT1-mediated actions; for example, while the AT1 receptor stimulates inflammation, the AT2 receptor has an anti-inflammatory effect. Ang-II binding to the AT2 receptor also induces vasodilation and enhances blood vessel remodeling.\textsuperscript{24} The activation of Ang-(1-7) is given by the MAS receptor, this regulatory axis has a biological importance because it counteracts the negative actions of Ang-II.\textsuperscript{35} It decreases the action of cytokines, interleukin (IL)-1β, IL-6, monocyte chemotactic protein-1 (MCP-1) and increases the expression of the anti-inflammatory cytokine IL-10. The Ang-(1-7) pathway is capable of activating the phosphatidylinositol 3-kinase (PI3-K) / protein kinase B (AKT) pathway, leading to the activation of nitric oxide synthase 3 (NOS3) and the generation of NO (Figure 2).\textsuperscript{38}

NO has initially been discovered as a pulmonary endothelial vasodilator gas that is widely used for cases with hypoxemia and as an arterial oxygenation enhancer.\textsuperscript{39,40} NO is a molecule produced by mammalian cells that fulfill the function of signaling between cells and is involved in neurotransmission, blood pressure control and cellular defense mechanisms caused by bacteria, viruses and others. NO also serves as a vascular mediator by limiting platelet activation, adhesion and aggregation, and deficiency of bioactive NO is associated with arterial thrombosis in tissues with endothelial dysfunction and patients with a deficiency of the extracellular antioxidant enzyme glutathione peroxidase-3.\textsuperscript{31}

Platelets are continuously exposed to activating factors (fibrinogen, ADP, factor, thrombin, thromboxane, etc.) as well as inhibiting factors such as endothelium-derived NO, PGI2 and ADPase. These activation and inhibition factors bind to specific platelet receptors and stimulate
signaling pathways that promote or inhibit platelet adhesion, aggregation, and secretion. When the MAS-NO axis is activated it strongly inhibits thrombus formation. NO plays the role of immune defense in the host and in the physiopathology of some clinical diseases, due to the wide susceptibility in its external manipulation. Furthermore, studies have shown that the release of NO at the vascular level induces diuresis and has a vasodilatory effect, favoring a decrease in blood pressure.

Inflammation and immune response

Pyroptosis is a form of programmed cell death with inflammatory effects. To trigger this process the presence of protein 3a is necessary. The subunit S2 of the SARS-CoV protein encodes four structural proteins, spike (S), envelope (E), matrix (M) and nucleocapsid (N), and other non-structural proteins, together with a group of accessory proteins that are expressed during the infection within them is the 3a consists of 274 amino acids. ORF 3a of SARS-CoV encodes a transmembrane protein 3a, also known as U274, X1 or ORF3, has been detected only in SARS-CoV infected lung cells, but not in other organs, and is not found in SARS-CoV negative patients. 3a is a cell membrane-associated protein that forms ion channels that are selective for potassium ions, this may also promote virus release, also found in the cytoplasm and nucleus of infected cells. In addition, it can perform the assembly functions of SARS-CoV. The outflow of K+ is an activator of the inflammasome resulting in increased permeability, which can occur through decreased cytosolic content of K+ and this acts as a trigger for inflammatory reactions such as NLRP3. Changes in intracellular ion levels trigger the activation of the inflammasome and the production of IL-1β in lung cells such as macrophages and lymphocytes.

The synthesis of IL-1β, IL-18 is initially found as an inactive precursor and requires excision of caspase-1 to process into an active molecule, then, activated caspase-1 splits the immature form of the proinflammatory cytokines into its mature form to increase the inflammatory response and finally leads to pyroptosis.

The immune responses to SARS-CoV-2 also involve a number of white cells, such as monocytes, which are key to the host's defense and can be found in all tissues of the body, including the respiratory system. Monocytes are cells that do not divide and have a short life span, which prevents viral replication, however, it is possible for the COVID-19 virus to enter the monocyte/macrophage through phagocytosis and this leads to the initiation of gene transcription and viral protein synthesis so it is important for the pathogenesis of the virus.

Monocytes can be the means of transport of the virus for dissemination to other tissues because of their wide concentration in the bloodstream, consequently the progression of the infection in humans.

In the presence of a viral infection, monocytes/macrophages are producers of cytokines/chemokines that attract the migration of neutrophils, macrophages and activated T-lymphocytes, which are involved in the immune response, the initiation of inflammation that can be modulated and used by the virus for the spread and establishment of the infection. At the onset of pneumonia, patients diagnosed with COVID-19 develop pulmonary edema with hyperplasia of the interstitium. For these reasons, the demand for assistance with mechanical ventilation is increasing worldwide. We maintain that the reasons why SARS-CoV-2 has a high affinity for lung tissues is because of the high number of receptors for the virus and limits the ability of these receptors (ACE2) to perform the functions of hydrolyzing Ang-II, thus triggering a serious alteration of molecular sequences to perform physiological functions.

CONCLUSION

The entry of the COVID-19 virus into humans occurs when it reaches cells containing ACE2 receptors, the main one being the upper respiratory tract (nasal mucosa), followed by the mouth (tongue, oral and gingival mucosa), and less frequently through the conjunctiva. The serious consequences of inflammation and thrombus formation in symptomatic patients caused by SARS-CoV-2, is largely due to the imbalance of regulation by diminishing ACE2 receptors, which serves to activate the regulatory axis Ang-II→ACE2→Ang-(1-7)→MAS receptor, which counteracts the negative actions caused by Ang-II. The ACE2 is also the main receiver for the SARS-CoV-2 so that it can trigger the virulence processes in the host.

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