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Open and Closed State of Spike SARS-COV-2: Relationship with Some Integrin-Binding. A Biological Molecular Approach to Better Understand the Coagulant Effect

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Abstract

Related the physio-pathological process of covid-19 disease it is interesting to focus to the aspect played by interaction of SARS-COV-2 protein with integrins of human epithelial pulmonary cell. A bio molecular approach help in to deeply verify the involved factors and the results of this activation RGD mediated of Great interest also the relationship with some vaccine strategy followed by the various pharmaceutical industry. The results of this work will be useful to think modification in some vaccine increasing the global safety and related some rare ADR.

Keywords: Physio-pathological • SARS-COV-2 • Pulmonary cell

Introduction

Observing literature related SARS-CoV 2 penetration in pulmonary epithelial cells it is reported a binding between Spike protein and ACE 2 receptor but other mechanism seem involved like by some integrin binding. "Surprisingly, the autopsies of COVID-19 patients have revealed clots in the small -vessels of the lungs, heart, liver, and kidney which are responsible for strokes and heart attacks [1]. More than 33% of critical COVID-19 patients' are reported with critically high- levels of blood -clotting or elevated levels of D-dimer. We can hypothesize and end with the conclusion that the mysterious -clots reported in the COVID-19 patients may be due to the binding of the spike- protein of SARS-CoV-2 with the ACE2 receptor expressed in the endothelial -cells of blood vessels which may cause, vaso-constriction and activation of the intrinsic- pathway of coagulation and eventually results in the formation of blood -clots. in COVID-19 patients, the SARS-CoV-2 mediated endothelial- inflammation, thrombin generation, platelet, and leukocyte recruitment, complement activation, and the initiation of innate and adaptive immune-responses, forming clots, culminate in immune-thrombosis, ultimately resulting in thrombotic- complications, stroke, and finally death".

"Proteolytic cleavage of the spike forms a barrier to zoonotic-crossover independent of receptor binding. Hemostasis is of central importance in mammals and represents a major vulnerability of mammals to predators and pathogens, either through hyper-activation of coagulation or uncontrolled bleeding. The dysregulation of hemostasis is a convergent mechanism of toxins of snakes, bees, and bats and a driver of virulence in Ebola and dengue virus infection disease. Perhaps, SARS-CoV-2 has undergone selection to both induce and exploit an environment locally enriched in coagulation proteases, instigating a positive feedback loop to promote entry into additional host cells" [2].

"Numerous signaling -pathways are mediated by integrins and virion binding could lead to dys-regulation of these pathways, with consequent tissue- damage. Integrins on the surfaces of pneumocytes, endothelial cells and platelets may be vulnerable to CoV-2 virion- binding. Binding of virions to integrins on endothelial-cells could activate angiogenic- cell signaling pathways; dysregulate integrin-mediated signaling pathways controlling developmental processes; and precipitate endothelial activation to initiate blood-clotting. Such a procoagulant state, perhaps together with enhancement of platelet- aggregation through virions binding to integrins on platelets, could amplify the production of micro-thrombi that pose the threat of pulmonary thrombosis and embolism, strokes and other thrombotic consequences. With viral- invasion, the activated endothelium would cause platelet adhesion and activation with coincident switching of integrin αIIbβ3 into a high-affinity conformation. Fibrinogen binds to activated integrin αIIbβ3 and is quickly converted to fibrin by the proteolytic activity of thrombin on the platelet surface. Platelet aggregation is then driven by binding of

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monomeric, oligomeric and polymeric fibrins to integrin αIIbβ3 molecules on adjacent platelets, linking them to one another in a rapidly growing clot.

Material and Methods

Based on data extracted from COVID-19 patients during the first 2 months of viral outbreak, 59.6% severe cases showed a feature of elevated D-dimer and average platelet- count in severe-COVID-19 patients appeared to be lower than that in non-severe group, which attracted much attention on coagulo pathy secondary to COVID-19. A retrospective cohort- study enrolling 191 cases was published at March 11th, which introduced the clinical course and risk -factors for adult deaths in COVID-19 patients in Wuhan, China. In this study, coagulation -dysfunction was found in 27 (50%) non-survivors of COVID-19, with elevated D-dimer and prolonged PT. In another work, with 183 cases enrolled and dynamic alterations in coagulation profiles recorded, Tang et al. reported a mortality of 11.5% in COVID-19 patients and they found 15 (71.4%) of the deaths ascribed to COVID-19 met the diagnostic criteria of overt disseminated intravascular- coagulation (overt-DIC, ≥ 5 points) based on the International Society On Thrombosis And Haemostasis (ISTH), but only 0.6% of the survivors matched the criteria. With an observational method some relevant biomedical literature is analysed. Some figures are reported to better explain the meaning of this work. An experimental project hypotesys is submitted to the researcher in order to produce a global conclusion [3].

Results

"S-protein is composed of two functional -subunits, including the S1 and S2 subunits. The S1 subunit consists of N-Terminal Domain (NTD) and Receptor Binding Domain (RBD). The function of S1 subunit is bind to the receptor on host cell. S2 subunit contains Fusion Peptide (FP), Heptad Repeat 1 (HR1), Central Helix (CH), Connector Domain (CD), Heptad Repeat 2 (HR2), Trans Membrane Domain (TM), and Cytoplasmic Tail (CT). The function of S2 subunit is to fuse the membranes of viruses and host- cells. The cleavage site at the border between the S1 and S2 subunits is called S1/S2 protease cleavage site. For all the coronaviruses, host proteases cleave the spike glycoprotein at the S2' cleavage site to activate the proteins which is critical to fuse the membranes of viruses and host cells through irreversible conformational changes. N-linked glycans are critical for proper folding, neutralizing antibodies, and decorating the spike- protein trimers extensively. The S -protein has two forms of structure, including the closed state and the open- state . In the closed state, the three recognition motifs do not protrude from the interface formed by three spike- protein protomers. In the open state, the RBD is in the "up" conformation. The open state is necessary for the fusion of the SARS-CoV-2 and the host cell membranes, thereby facilitating SARS-CoV-2 to enter the host cells [4].

One study work obtained a 3.5 Å-resolution structure of spike-protein trimer with one RBD in the in the "up" conformation (receptor-accessible state). Receptor- binding destabilizes the prefusion structure, triggered by this process, the S1 subunit dissociates and the S2 subunit refolds into a stable post-fusion conformation, which has been captured in SARS-CoV. RBD goes through conformational -transitions like a hinge, leading to the hide or exposure of the determinants of the spike- protein to engage a host cell receptor. This process will form the following 2 states: "down" conformation and "up" conformation. In the "down" conformation, SARS-CoV-2 could not recognize the ACE2 on the host- cells. The structure of SARS-CoV-2 is highly similar with SARS-CoV. One of the larger differences is in the down -conformation, SARS-CoV RBD packs tightly against the NTD of the neighboring protomer, while the angle of SARS-CoV-2 RBD is near to the central- cavity of the spike -protein trimer. When aligned the individual structural- domains corresponding to SARS-CoV-2 and SARS-CoV, highly similar structures were observed.

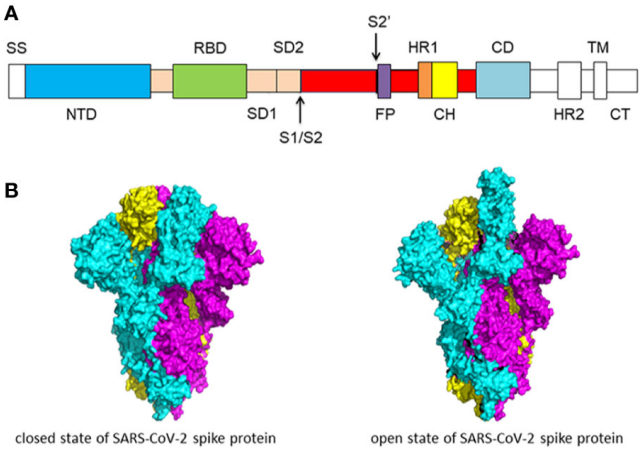

Figure 1: A) Schematic of SARS-CoV-2 spike- protein primary-structure. Different domains are shown by different colors. SS, single-sequence; NTD, N-terminal domain; RBD, receptor-binding domain; SD1, subdomain 1; SD2, sub-domain 2; S1/S2, S1/S2 protease cleavage- site; S2', S2' protease cleavage site; FP, fusion peptide; HR1, heptad repeat 1; CH, central helix; CD, connector -domain; HR2, heptad repeat 2; TM, transmembrane- domain; CT, cytoplasmic tail. The protease cleavage site is indicated by arrows. B) Cryo-EM structure of the SARS-CoV-2 spike protein. The closed- state (PDB: 6VXX) of the SARS-CoV-2 S glycoprotein (left) the open state (PDB: 6VYB) of the SARS-CoV-2 S glycoprotein (right).

"HCoVs are positive-sense, single-stranded RNA- viruses and 30,000 bp long. 2 types of proteins are identified in HCoVs: four structural- proteins including Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins and non-structural proteins, like proteases and RNA dependent-RNA polymerase. The S protein is a pivotal -tool for virus- adhesion and entry into host -cells and it can represent an intriguing target for the development of antibodies, entry inhibitors or vaccines. It is present on the virion's outer surface and displays a homo-trimeric state. Protein S allows viral entrance into host- cells by firstly binding to a host -receptor, such interaction occurring through the Receptor Binding Domain (RBD) in subunit S1, and secondly through subunit S2 the viral and host -membranes fuse. Similar to SARS-CoV, SARS-CoV-2 also recognizes Angiotensin-Converting Enzyme 2 (ACE2) as its host receptor -binding . The variation of crucial residues in S-protein of SARS-CoV-2 may contribute to the highly-transmission efficiency of the virus. The reported evolutionary-mutation of K403R in S1 protein of SARS-CoV-2 forms an RGD motif in RBD at the interaction -surface neither been found in Bat RaTG13 nor in SARS-CoV.

The RGD motif is the cell attachment site of a great amount of adhesive extracellular- matrix and cell surface proteins and is recognized by the membrane receptor- integrins. The integrins are

hetero-dimers of α- and β-subunits linked in a non-covalent manner and play key functions in cell adhesion, cell-cell interactions, signaling and defense- mechanisms.

Human meta-pneumo-virus is similar to SARS-CoV-2 regarding the organ tropism and symptoms, and its protein F's RGD triade displays a fold comparable to that of SARS-CoV-2. Integrins play an important role in different respiratory -diseases, in particular in pneumonia resulting from bacteria or virus-infections.

Upon the binding, the RBD of S1 subunit undergoes a conformational shift and this change exposes or hides the key- region of binding -domain to access to ACE2. The RGD motif would be exposed to the surface of the host cell- membrane with the key binding region and thus prones to interact with integrin.

Biomedical -Literature data show that also ACE2 displays a conserved RGD motif and it is able to bind integrin- subunits. The binding seems to be RGD-independent because of the in-accessibility of the motif, letting to speculate that thanks to a conformational shift the site could be exposed, enhancing cell adhesion and therefore justifying the higher infectivity" [5].

S2 subunit N-linked glycosylation is mainly conserved in SARS-CoV S glycol-proteins, indicating that the availability of the viral-fusion machinery is comparable between these viruses. Recent evidence has been published showing low levels of O-glycosylation in SARS-S protein.

These oligo-saccharides contribute to S protein folding, impinge on priming by host proteases, and regulate antibody recognition. Low levels of O-linked glycosylation have been detected, suggesting that O-glycans of this region are insignificant when the structure is native- like.

The presence of O-glycans in some viral proteins suggests an important role in biological -activity. In the SARS-CoV-2 S1, the O-type glycosylation by O-GalNAc and O-GlcNAc seems to be involved in protein stability and function.

The S glycoprotein is a target in vaccine -design; the changes in the glycosylation of viral- spikes can disclose important elements for the knowledge of viral -biology and facilitate vaccine- design strategies.

"We identified an RGD/KGD integrin-binding motif in S- proteins from SARS-CoV-2 and SARS-CoV. We also discovered a KGD integrin-binding motif in ACE2.

Integrins were predicted to inhibit receptor targeting of S proteins from SARS-CoV-2 and SARS-CoV by shielding both S- protein and ACE2. Integrins are hetero-dimeric proteins comprising α and β subunits in cell- surface.

Many integrins recognize Arg-Gly-Asp (RGD) and Lys-Gly-Asp (KGD) motifs which are displayed on the exposed- loops of proteins. RGD could associate broader types of integrins such as αVβ1, αVβ3, αVβ5, αVβ6, αVβ8, αIIbβ3, αMβ2, αLβ2 and α3β1, while KGD-recognizing integrins are restricted to αIIbβ3, αVβ5, αVβ6 and αVβ8.2".

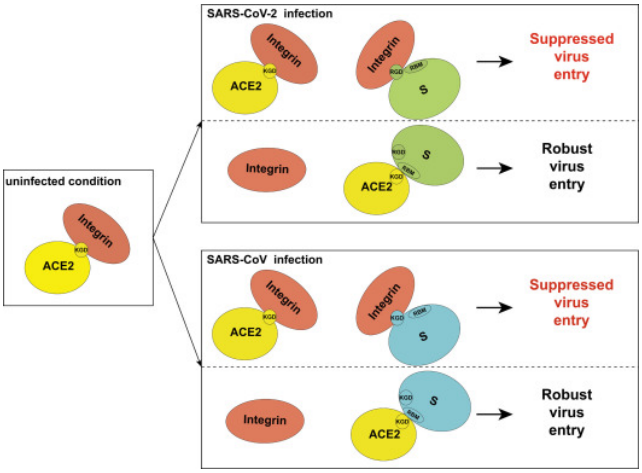

Figure 2: Proposed model for the inhibitory role of integrin in SARS-CoV-2 and SARS-CoV.

Discussion

In this article are reported figure and reference related RGD motif of spike protein and the ability of this to link also some integrin like fibronectin. The same literature link viral load to a pro-trombotic status in the moderate severe covid-cases. Integrin like fibronectin is physiologically involved in coagulation process as reported by many scientific literatures. But what is relevant is to verify if there is a quantitative relationship between spike protein and procoagulant status and to to do this the verify of relationship viral load and the Trombosys event is crucial. The same it is interesting to verify the level of spike traduced after a vaccination and to compare this with the covid severe disease level.

Conclusion

Researcher verify that the covid-19 virus not only bind ACE2 receptor but also some integrins like fibronectin. In this process The RGD motif play a crucial role and also the status of OPEN or CLOSED to bind in efficient way. Scientist find relationship between viral load and severity. For disease and related the activation of blood coagulation. Finally it is interesting to observe that in some RARE adverse event of some covid-19 vaccine a trombosys event was observe. So in by the opinion of the author it is needed to verify in vitro the procoagulant effect level after Covid-19 Vaccination.

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