Info Authors :

[1] Senior Registrar, Department of Otolaryngology-Head & Neck Surgery, Mahatma Gandhi Memorial Medical College and M.Y. Hospital, Indore, M.P, India. Member, Association "Naso Sano" Onlus, Umbria Regional Registry of volunteer activities, Corciano, Italy.

[2] Consultant, Department of Anesthesiology, Raja Isteri Pengiran Anak Saleha Hospital , Brunei Darussalam.

[3] Chief of the Unit of Internal Medicine, Department of Medicine, University of Perugia, Hospital " Santa Maria della Misericordia", Perugia, Italy.

[4] Consultant , Emergency department, Usl Umbria 1, Perugia, Italy.

[5] Founder and President, Association "Naso Sano" Onlus, Umbria Regional Registry of volunteer activities, Corciano, Italy
Department of Otolaryngology-Head & Neck Surgery, Gubbio-Gualdo Tadino Hospital, USL Umbria 1, Italy.

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KEY ROLE OF ANNEXIN A2 AND PLASMIN IN COVID-19 PATHOPHYSIOLOGY, CLINICAL PRESENTATION AND OUTCOMES - A REVIEW

Asiya Kamber Zaidi [1], Sunny Dawoodi [2] , Matteo Pirro [3] , Manuel Monti [4], Puya Dehgani-Mobaraki [5]

REVIEW

ABSTRACT

The Coronavirus disease 2019 (COVID-19) pandemic has become a defining global health crisis with an exceptionally high rate of transmission causing significant morbidity and mortality.

Recent studies have reported patients presenting with coagulation disorders and thrombo-embolic disease later testing positive for the coronavirus.

In this article, we have discussed the recent trend in symptomatology of COVID-19 including microvascular thrombosis and the potential key role of proteins such as Annexin A2, plasmin, ACE-2 receptors and ENaC channels in the disease pathophysiology.

The interactions between these molecules and the viral proteins might play a role in thrombo-embolic presentation of the disease and explain the selective morbidity in patients with co-morbid conditions.

A diagrammatic working model has also been proposed that shall assist readers in understanding these key bio-molecular interactions influencing the probable pathophysiology at the cellular-receptor level.

This article shall also shed some light on the genetic polymorphisms in ACE-2 receptors and Annexin A2 suggesting a possibility of extensive diversity in clinical presentation and disease severity across the globe.

Evidence-based studies might guide in identifying potential therapies and treatment options for COVID-19.

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BACKGROUND

The Coronavirus disease 2019 (COVID-19) has emerged as a pandemic caused by a new beta-coronavirus, SARS-CoV-2.

Reports have suggested the epicenter of this disease to be Wuhan, China, with an ominously high rate of transmission. Sequencing of a large number of SARS-CoV-2 virus isolates have revealed a close relationship of SARS- COV-2 with two bat-derived coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21.[(1)]

In order to replicate effectively, viruses essentially takeover and reprogram the host cells to produce viral progenies. The life cycle of a virus consists of three main phases:

(a) Cellular attachment and penetration through receptor-mediated endocytosis or direct membrane fusion.

(b) Release of the viral genome for replication and protein expression. This depends on host enzymes that facilitate capsid uncoating or the host machinery to replicate the viral genome.

(c) Assembly and maturation yielding newly constructed viral particles primed for release after post-translational modification by host factors.

The four key viral proteins essential in COVID-19 pathogenesis

The S proteins bind to the ACE-2 receptors after being cleaved by furin-like proteases.

The RNA-dependent RNA polymerase (RdRp) is responsible for SARS-CoV-2 RNA genome replication. The 3C-like and papain-like proteases cleave the two polyproteins important in packing of the new virions. [(1)]

The S protein of the SARS-CoV-2 binds to human ACE-2 receptors with higher affinity as compared to the other SARS-CoV viruses. [(2)]

As per Coutard B et al. the spike glycoprotein of the new coronavirus SARS-CoV-2 contains a furin-like cleavage site absent in other coronaviruses of the same clade.

This special site (682RRAR/S686) inserted in the S1/S2 protease region of the virus has been suggested to play a role in the increased affinity. [(3)] (Figure 1)

The S1 region of the Spike protein is responsible for binding with host cell ACE-2 receptor, while the S2 region is responsible for the fusion of the viral RNA and cellular membranes.

Amongst the cluster of the furin-cleaved viruses, the SARS S protein is cleaved by the airway proteases (trypsin, plasmin, and TMPRSS family), expressed by human bronchial epithelial cells subsequently enhancing the virus entry by binding with the host ACE-2 receptors. [(4)]

As demonstrated in vitro, a serine protease inhibitor for TMPRSS-2 blocks the SARS-CoV-2 S protein-driven entry into the cells. [(5)]

Camostat mesylate, a serine protease inhibitor has been approved for clinical use in Japan for COVID-19.

It acts by inhibiting the host cell serine protease TMPRSS2 , required for priming the viral S protein for cell entry.

It might also play a beneficial role by partially inhibiting plasmin. [(6)]

The recent changing trend in the clinical presentation of COVID-19 Coexistence of coagulation system activation and hyperfibrinolysis

In addition to the known common clinical presentation of COVID-19 infection including high fever, sore throat, dry cough, breathing difficulties ,malaise and GI symptoms such as diarrhea, few reports have also demonstrated a state of dynamic hypercoagulation and a strong association between elevated D-dimer levels and poor prognosis.

(a) Venous thromboembolism (VTE)

There have been recent case reports on

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thromboembolic disease, stroke and myocarditis in patients with COVID-19 [7] [10].

In a retrospective study by Chen J et al. on 1008 patients, out of 25 patients who underwent CT pulmonary angiography, ten patients (40 %) demonstrated acute PE mainly located in the subsegmental vessels.

These patients were treated with anticoagulant therapy. On follow up , three patients demonstrated partial or complete resolution on CT pulmonary angiography, while two patients succumbed. [8]

(b) Disseminated intravascular coagulation (DIC)

In a Chinese single-center retrospective cohort study at the Tongji hospital, a total of 183 patients with confirmed COVID-19 were evaluated for DIC. [11]

As per the definition of DIC by the International Society on Thrombosis and Hemostasis, 15 out of the 21 non-survivors (71 %) had suffered from overt DIC (≥5 points) during the follow-up.

(c) Microvascular Thrombosis

Recent observations have also suggested that the respiratory failure in patients with COVID-19 is not only driven by the development of the acute respiratory distress syndrome (ARDS) alone [12], but microvascular thrombotic processes may play a significant role as well.

One series by Zhang T et al. [13] described the pulmonary histopathology in SARS1 (N=44) and SARS2 (COVID-19) (N=4) patients. Both infections showed diffuse alveolar damage, pulmonary microvascular thrombosis and necrosis in mediastinal lymph nodes and the spleen.

However, it was interesting to note that only COVID-19 patients showed small vessel thrombosis in multiple organs. [13]

(d) D-dimer levels

The cross-linked fibrin degradation products, D-dimers reflect blood clot formation and its subsequent fibrinolysis.
They have very high sensitivity for thrombotic disease, but the specificity is poor.

Various studies in patients with COVID-19 have consistently shown a very strong association between increased D-dimer levels and severe disease/poor prognosis. [8] [14] [15] [16]

(e) Large vessel stroke

A correspondence in the NEJM (dated April 28, 2020 DOI: 10.1056/NEJMc2009787) reported five cases of large-vessel stroke in patients younger than 50 years of age presenting to a healthcare system in the New York City.
SARS-CoV-2 infection was diagnosed in all five patients.

Another retrospective study of data from the COVID-19 outbreak in Wuhan, China, showed the incidence of stroke among hospitalized patients with COVID-19 to be approximately 5% ; the youngest patient in that series was 55 years of age. [17]

It should be noted that , coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19.[14]

Similar to studies by Flanagan et al in 2011 on the genetic predictors for stroke in children with sickle cell anemia , polymorphisms in the ANXA2 gene might be associated with an elevated risk of stroke and pulmonary hypertension in certain group patients while not in others with COVID-19. [18]

The Annexin A2/S100A10 System

The (A2-p11)2 assembly : Annexin A2 (AnxA2) is a pleiotropic protein belonging to the annexin family of Ca2 + -regulated phospholipid binding proteins, "expressed in plants, animals, and protists throughout the phylogenetic tree". [19]

AnxA2, a 36-kilodalton protein is produced by endothelial cells, monocytes, macrophages, trophoblast cells, and some tumor cells. [20] [21]

The human AnxA2 gene is present on the chromosome 15 (15q21).[22]

When AnxA2 is membrane linked, the tightly packed, alpha-helical core domain forms a disk with its convex surface associated with membrane

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phospholipids and the concave surface oriented away from the membrane.
Membrane binding is mediated by at least two potential Ca2+ -binding "annexin" repeats, a feature common to all annexin family proteins. (21)

While the core domains of the annexin proteins are relatively well conserved, the hydrophilic amino-terminal "tail" or "interaction" domains are highly variable and essentially unique to each family member. The tissue plasminogen activator (tPA) binds at the tail end of Annexin A2.

Another molecule, the Protein S100A10, also known as p11, is a well-described binding partner of AnxA2. (23) (24)

With this binding partner S100A10 (p11) and AnxA2 form a cell surface complex that regulates generation of the primary fibrinolytic protease, plasmin, and it is dynamically regulated in settings of hemostasis and thrombosis. [Figure 1]

In addition, it should be noted that, this complex is transcriptionally upregulated in hypoxia.
This might probably play a role in triggering and further cascading the thrombotic complications following hypoxia in COVID-19.

A study conducted by Kim J et al. on "Annexin II: a plasminogen—plasminogen activator co-receptor" defined the concept of fibrinolytic assembly as "A central tenet of cell surface fibrinolysis" , in which the tPA dependent conversion of plasminogen to active plasmin is precisely orchestrated through the formation of a multimolecular complex consisting of tPA, the annexin A2 heterotetramer, and plasminogen. (25)

Annexin A2 along with its binding partner p11, forms a heterotetrameric (A22-p112) receptor for both plasminogen, the inactive precursor of plasmin, and its activator, tPA. By assembling tPA, annexin A2, and plasminogen, this complex increases the catalytic efficiency of tPA, enabling it to convert plasminogen to plasmin at least 60 times more efficiently than the same amount of tPA alone. (25) (26)

Association between elevated plasmin levels , ACE-2 receptors, D-dimer levels and ENaC channels in COVID-19 patients with co-morbidities

In a review by Ji HL et al elevated Plasmin(ogen) was identified as a common risk factor for COVID-19 susceptibility.

In addition, increased plasmin levels were demonstrated in COVID-19 positive patients with comorbidities such as hypertension , diabetes, ARDS , cardiovascular disease, chronic kidney disease, cerebrovascular disease. (1)

Few interesting points from the review are as follows:

- Plasmin, as a key player in fibrinolysis, enhances the virulence and pathogenicity of viruses that contain a furin site in their envelope proteins, as is the case with the SARS-CoV-2.

- Plasmin also cleaves the S protein of SARS-CoV 2 extracellularly, increasing its ability to bind with angiotensin converting enzyme 2 (ACE-2) receptors of host cells, probably facilitating virus entry and fusion.

- Plasmin proteolytically breaks down excess fibrin (hyperfibrinolysis) to elevate the D-dimer levels and other fibrin degradation products in both bronchoalveolar lavage fluid and plasma ,which decreases platelets and further results in hemorrhage.

- Plasmin also cleaves the epithelial sodium channel (ENaC) subunits, located at the apical membranes of epithelial cells in the airway, lung, and kidney.

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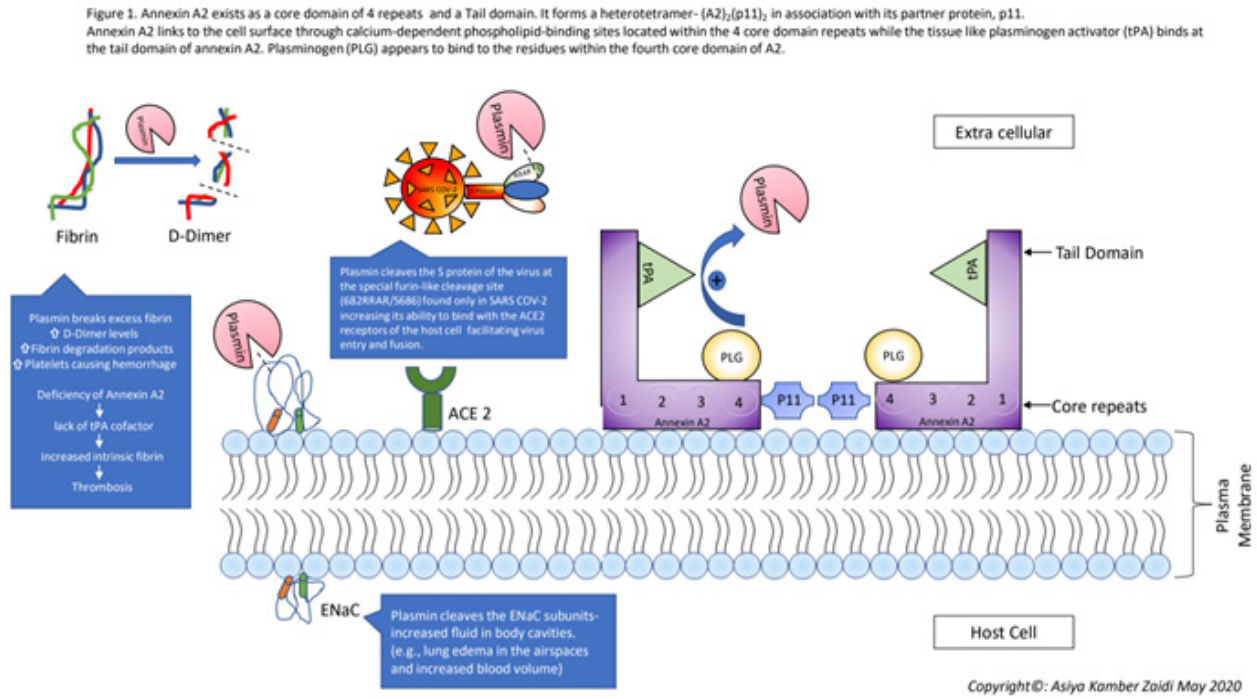
FIGURE 1



Annexin A2 exists as a core domain of 4 repeats and a Tail domain.
It forms a heterotetramer- $(A2)_2(p11)_2$ in association with its partner protein, p11. Annexin A2 links to the cell surface through calcium-dependent phospholipid-binding sites located within the 4 core domain repeats while the tissue like plasminogen activator (tPA) binds at the tail domain of annexin A2. Plasminogen (PLG) appears to bind to the residues within the fourth core domain of A2.

Association between ACE-2 polymorphism and SARS-COV

It is important to underline that SARS-CoV-2, like many other viruses, enters the cells through ACE-2 receptors.[5]

The ACE-2 receptor is almost "ubiquitous" but nevertheless, 83% of the cells expressing ACE-2 seem to be type 2 pneumocytes.

In a recent study, SARS-CoV-2 was found to destroy mainly type I pneumocytes. [27]

However, few studies have suggested that ACE-2 expression could be specific to certain populations and might lead to variation in expression levels thereby altering the susceptibility, symptoms, and outcomes of COVID-19 infection. [28] [29]

A study by Li et al. demonstrated that some ACE-2 variant could reduce the association between human ACE-2 and SARS-CoV S-protein. [28]

Moreover, in a study by Cao Y et al. a comparison of the 15 expression quantitative trait loci (eQTLs) variants of the ACE-2 gene suggests that there are a lot of ACE-2 polymorphisms causing diverse ACE-2 expression levels in the Asian and European populations. [29]

This might be a probable reason for variations in susceptibility, morbidity and mortality figures across the globe.

On the same lines, polymorphisms in the Annexin A2 gene may also play a role in variations in expression of annexin A2 and this requires further studies.

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In vivo animal studies on annexin A2 and vascular homeostasis

The Annexin A2 deficient (*AnxA2* –/–) mouse has been highly informative in investigating the role of the annexin A2 system in vascular homeostasis in vivo.

Although these A2-deficient mice displayed normal development, fertility, and lifespan, fibrin accumulation was evident in both intravascular and extravascular locations within the lungs, spleen, small intestine, liver, and kidney. [(30)]

Microvascular endothelial cells isolated from *AnxA2* –/– mice, moreover, lacked the ability to support tPA- dependent plasmin generation in vitro, and arterial injury in vivo lead to an increased rate and severity of vascular occlusion in the *AnxA2* –/– mouse.

Recently, fibrinolysis was also assessed in p11-null mice, which also displayed increased vascular fibrin, reduced clearance of thrombi, and impaired neovascularization of Matrigel thrombi. [(31)]

It was also interesting to note that , mice with diet-induced hyperhomocysteinemia shared the phenotypic feature with the *AnxA2* –/– mouse. [(32)]

Elevated levels of homocysteine (HC), a thiol-containing amino acid generated during the conversion of methionine to cysteine has been associated with both thrombotic and atherosclerotic vascular disease. [(33)]

Role of Annexin A2 in modulating frameshifting efficiency of the virus

A study by Hoyun Kwak et al. identified AnxA2 as a RNA binding protein (RBP) that binds IBV (Infectious Bronchitis Virus) pseudoknot RNA in vitro and also in the cells confirmed by ultraviolet crosslinking.

The results suggest that AnxA2 is a cellular RBP that can modulate the frameshifting efficiency of viral RNA, enabling it to act as an anti-viral cellular protein, hinting at its role in RNA metabolism for other cellular mRNAs. [(34)]

Role of Annexin A2 in causing olfactory disturbances and neurological manifestations in COVID-19

Coronavirus has already been identified as a family of viruses that may be associated with anosmia.

A landmark paper by Xydakis MS et al on the Smell and taste dysfunction in patients with COVID-19 mentions reports from ear, nose, and throat (ENT) surgeons and other health-care workers at the front lines with complains of anosmia with or without dysgeusia as a symptom frequently associated with (SARS-CoV-2) infection.

The American Academy of Otolaryngology—Head and Neck Surgery and the British Association of Otorhinolaryngology are now recommending these symptoms be added to the list of primary screening symptoms for COVID-19. [(35)]

The WHO has also now included 'loss of smell or taste' as one of the symptoms of COVID-19. (source: EPI-WIN: WHO information network for epidemics) since 4th of May 2020.

In a study by Helene Debat et al, a proteomic approach was used to identify the proteins in the "Human Olfactory Cleft Mucus" and the nature of these proteins was determined using two-dimensional gel electrophoresis (2-DE), MALDI-TOF, RPLC, and Edman sequencing. Annexin A2 and Plasminogen binding protein were identified as the constituent protein molecules from a complex list of 82 proteins in the olfactory mucus. [(36)]

It has also been demonstrated that dicalcin and annexins are colocalized in the olfactory and respiratory cilia which are motile.

These motile cells are often subjected to "mechanical stress and damage" [(37)] while being exposed to environmental chemicals, microorganisms and viruses.

In such cases, the "membrane of the cilia is often likely to be damaged and disrupted". [(38)]

This membrane aggregation can be regulated

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by these complexes within a range of Ca2+ concentration by using two annexin subtypes. This mechanism might help in resealing the cilia membrane in response to a wide range of Ca2+ increase caused by the disruption of these membranes. [39]

Considering the possible role of annexin A2, present in the olfactory mucus and its key role in membrane organization and stabilization, we hypothesize that it might also play a key role in the pathogenesis of olfactory disturbances in patients with COVID-19.

In 2007, Suzuki et al. [40] also demonstrated that coronavirus may be detected in the nasal discharge of patients with olfactory dysfunction.

The ability of human coronavirus to invade the olfactory bulb and therefore, the central nervous system, is most likely a topic for future research. It has been demonstrated on transgenic mice that SARS-CoV might enter the brain through the olfactory bulb, leading to a rapid transneuronal spread.

Interestingly, authors demonstrated that the virus antigen was first detected 60 to 66 hours post-infection and was most abundant in the olfactory bulb. Regions of the cortex (piriform and infralimbic cortices), basal ganglia (ventral pallidum and lateral preoptic regions), and midbrain (dorsal raphe) were also strongly infected after the virus had spread [41]; these regions are connected with the olfactory bulb.

Neurologic manifestations in COVID -19 fell into 3 categories:
Central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment, hearing loss and nerve pain), and skeletal muscular injury manifestations. [42]

Association between IL-6 causing cytokine storm, Annexin and D-dimer levels in COVID-19

A recent study by Tobias Herold et al. [43] revealed the level of IL-6 as a predictor of respiratory failure in hospitalized symptomatic COVID-19 patients .

In this study, elevated interleukin-6 (IL-6) was strongly associated with the need for mechanical ventilation (p=1.2.10-5).
In addition, the maximal IL-6 level (cut off 80 pg/ml) for each patient during the disease predicted respiratory failure with high accuracy (p=1.7.10-8, AUC=0.98).
Also, the risk of respiratory failure for patients with IL-6 levels of ≥ 80 pg/ml was 22 times higher compared to patients with lower IL-6 levels.

A study by Michot et al. (March 2020) [44] reported first successful treatment of a patient with respiratory failure related to COVID-19 with Tocilizumab, an anti-interleukin 6 receptor drug (dosage : two doses of tocilizumab, at 8 mg/kg intravenously for each dose, 8 hours apart).

High plasma levels of proinflammatory cytokines (interleukin-2, interleukin-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A and tumor necrosis factor-α) have been observed in COVID-19 patients admitted to intensive care units. This is consistent with a "cytokine storm" with the secondary development of a hemophagocytic lymphohistiocytosis. [45] [46]

While many pro-inflammatory cytokines trigger the coagulation system, Zhou and colleagues [14] showed that the increase in IL-6 was discrepant with the elevations in D-dimer; IL-6 levels appeared to increase only 13 days after the disease onset, whereas D- dimer levels were already 10-fold increased by that time.

This observation probably suggests that high D-dimer levels in COVID-19 patients was not only secondary to systemic inflammation, but might also reflect true thrombotic disease, induced possibly by the cellular activation triggered by the virus. Furthermore, it is possible that the increase in cytokines only represents an "epiphenomenon secondary to the dramatic damage to type I pneumocytes".

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In the study published by the Chinese group of HUI it is underlined that the immune response by SARS CoV-2 is lower than the immunological response that has been highlighted in the study of other viruses such as H5N1, H1N1, MERS-CoV and this could demonstrate that the increase in the D-dimer levels is mainly caused by direct thrombotic damage. (25)

Finally, Brichory et al. in 2001 demonstrated upregulated expression of annexin A2 caused by IL-6 and production of autoantibodies against annexin A2 was observed in lung cancer patients.

This association between IL-6 and Annexin A2, might have a significant role in patients with cytokine storm mainly due to IL-6. (47)

It has also been observed that IL-6 and IFN-γ upregulate epithelial cell surface expression of annexin A2 and enhance the epithelial cell-binding activity of anti-S2. (48)

Some limitations and points to ponder

The S2 protein in SARS-COV virus shows sequence homology with self- antigens and the potential pathogenic role of the cross-reactivity of anti- S2 remains a concern.

The local alignment by JEMBOSS-Water analysis showed that the sequence similarity between annexin A2 and two regions on S2 (residues 927–937 and residues 940–951) are 50 and 66.7%, respectively.

Results of the study by Fang YT et al. strongly suggests that SARS-CoV-induced autoimmunity raises an alert not only for effective therapy but also for the development of a safe vaccine.

Also, the SARS- associated cytokine storm may upregulate the expression of autoantigens.

In addition to annexin A2, the roles of other candidate autoantigens found in this study identified by proteomic approach remain to be further investigated.(48)

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