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The pathobiological harmony between the local pulmonary/bone marrow RAS and its management via tissue-RAS modulating agents in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an unprecedented threat to public health and healthcare systems. It presents unusual pathophysiological effects mainly characterized by immune-inflammatory response and prothrombotic state causing acute respiratory distress syndrome and multiple organ failure. SARS-CoV-2 enters target cells after binding to the angiotensin-converting enzyme 2 (ACE2) receptor and therefore has a direct effect on the renin-angiotensin system (RAS). Apart from affecting numerous organs including lungs, heart, gastrointestinal system, spleen, brain and kidneys, the spike protein of SARS-CoV-2 could attack hematopoietic stem cells and hematopoietic progenitor cells in bone marrow (BM) microenvironment together with the precursor and mature blood cells. Within this hematopoietic viral spread context, it is crucial to search the clinicopathological correlations of COVID-19 in order to develop specific potential therapeutics against pleiotropic SARS-CoV-2 actions. Therefore, pharmacological disruption of the pathological cross-talk of local BM RAS and pulmonary RAS via administration of the tissue-RAS modulating agents such as soluble ACE2, angiotensin (1-7), TXA127 and MAS receptor agonists may prevent the clinical progression of the COVID-19 syndrome via reducing the hematopoietic virus propagation and systemic multi-organ spread.

Keywords: COVID-19, SARS-CoV-2, ACE2, renin-angiotensin system, bone marrow

INTRODUCTION

The genesis of immunoinflammatory prothrombotic COVID-19 syndrome takes place following the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). COVID-19 can affect multiple organ systems, and in particular, its impact on the respiratory tract has led to an increase in morbidity and mortality worldwide (3). Systemic COVID-19 syndrome could affect numerous organs including lungs, heart, gastrointestinal (GI) system, brain, kidneys, and bone marrow (BM) with the exaggerated or disproportionate immunological activation. SARS-CoV-2 virus or its spike protein attacks on hematopoietic stem cells (HSC), hematopoietic progenitor cells (HPC), together with the precursor and mature blood cells (4-6). Within this hematopoietic viral spread context, it is crucial to search the clinicopathological correlations of COVID-19 in order to develop specific potential therapeutics against pleiotropic SARS-CoV-2 actions (2,4,7).

COVID-19 syndrome has three clinicopathological courses comprising initial, propagating and complicating phase (8). Each of these phases includes unique characteristics in relation to distinct immunogenomic mechanisms affecting critical tissue-based renin-angiotensin system (RAS) genes (9). The circulating RAS is usually considered as an endocrine system, however there are also numerous local tissue RASs within many organs, such as the BM, lung, kidney, heart, pancreas, brain, liver, GI tract and muscles (10,11). Being an important component of RAS, angiotensin-converting enzyme 2 (ACE2) which is a 40 kb gene positioned on chromosome Xp22 counteracts the adverse effects

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of angiotensin II. The ACE2 enzyme is found in high levels especially in lung alveolar tissue, nasopharyngeal tissue, enterocytes, vascular tissue, nervous tissue, and the kidney, nearly all points of potential viral entry for SARS-CoVID-2 (12). ACE2 transcription is enhanced during the initial phase of COVID-19. ACE2 molecule is the critical receptor of SARS-coronaviruses to enter the target cells (13). SARS-CoV-2 entry to human cells requires binding to the ACE2 receptor and utilizing a spike protein (S) for attachment. The viral S protein must be primed by transmembrane protease 2 (TMPRSS2) to facilitate interaction with ACE2 receptor and the subsequent fusion of viral and cellular membranes (14). ACE2 receptor is expressed on the surface of hematopoietic stem/ progenitor cells within the context of local BM RAS, which represents a target for the SARS-CoV-2 attack on BM hematopoiesis (5).

This review aims to demonstrate the pathobiological harmony between local pulmonary RAS and tissue hematopoietic BM RAS during the immunogenomic progression of the multi-systemic COVID-19 syndrome. Furthermore, the possible role of RAS modulating agents such as soluble ACE2, angiotensin (1-7), TXA127 and MAS receptor agonists will also be discusses as an alternative treatment alternatives against COVID-19 in order to reduce hematopoietic virus propagation and systemic spread.

Local Pulmonary RAS and COVID-19

Local tissue-based RAS significantly impacts on the injury/repair response within distinct organ/tissue systems. In this context, local pulmonary RAS is an already established regulator of the lung epithelial and endothelial cells (15,16). Through a combination of the circulating and tissue homeostatic systems, the local tissue RAS affects cellular biological events in the lungs. Local RAS activation within the pulmonary circulation and lung parenchyma could influence the pathogenesis of the lung injury via numerous mechanisms including a substantial increase in vascular permeability, vascular tonus and fibroblast activity, and by decreasing alveolar epithelial cell survival (15). Pulmonary ACE2 plays a pivotal role in protecting the lung from Ang II-AT1R induced inflammation because not only is there a local pulmonary RAS but the lung is also the major site for conversion of inactive Ang I to Ang II (17,18). Therefore, loss of the ACE2, following the binding of SARS-CoV-2, not only exposes the lung tissue epithelium to locally produced Ang II as well as to Ang II produced in the lung from circulating Ang I.

SARS-CoV which is very similar to SARS-CoV-2, and ACE2 interactions have been extensively studied in lung microenvironment (13,19-21). The first genetic proof whether ACE2 is indeed crucial for SARS-CoV infections in vivo was investigated by Kuba et al (13). It has been reported that SARS-CoV infections lead to the ACE2 down-regulation by the binding of the SARS-CoV spike protein to ACE2. Thus, the SARS-CoV family, including SARS-CoV-2, utilizes ACE2 as a critical receptor to enter target host cells. This loss of ACE2 expression resulted in severe acute respiratory failure. Recently in a study by Turk et al. (9) the whole-genome expression data of the lung epithelial cells infected with SARS-CoV for 12, 24, and 48 hours were analyzed, and a total of 15 RAS family and 29 immune genes were found to be highly associated with the exposure time to the virus in the studied groups. This finding strongly suggests the crucial role of the RAS genes on the initiation of the infections caused by coronavirus family members in the lung ecosystem.

Local Bone Marrow RAS, Hematopoietic Stem/ Progenitor Cells and COVID-19

Despite the obvious fact that the local pulmonary RAS is a major victim of the SARS-CoV-2 related immune dysregulation and cytokine release via ACE2, there is scarce evidence depicting the role of BM RAS in the progression of SARS-CoV-2 infection. Locally active RAS in the BM that affects the growth, production, proliferation, and differentiation of hematopoietic cells. The interactions of hematopoietic RAS with other tissue RASs are evident (10,11,22,23). All of the major RAS molecules including renin, angiotensinogen, angiotensin receptors and ACE are located within the BM microenvironment. Being the entry receptor for SARS-CoV-2, ACE2 expression has also been described in several types of cells including hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs). In a recent study by Ratajczak et al (14), ACE2 and the entry-facilitating transmembrane protease TMPRSS2 are reported to be expressed on very small CD133+CD34+Lin-CD45- cells in human umbilical cord blood, which can be specified into functional HSCs and EPCs. Moreover, the authors demonstrated that in human small embryonic-like stem cells (VSELs) and HSCs, the interaction of the ACE2 receptor with the SARS-CoV-2 spike protein activates the Nlrp3 inflammasome, which if hyper-activated may cause to cell death by pyroptosis. Therefore, human VSELs residing in adult tissues could be damaged by SARS-CoV-2, with remote effects on tissue/organ regeneration.

Recently, Kucia and coworkers demonstrated that ACE2 receptor is expressed on the surface of Hematopoietic Stem/Progenitor Cells, for SARS-CoV-2 viral entry (5). In their experiments; CD34+CD133+lin–CD45–, CD34+Lin–CD45+ HSCs and CD34+ CD133+ KDR+ CD31+ EPC cells were phenotyped for the expression of ACE2 and the SARS-CoV-2 entry-facilitating transmembrane protease TMPRSS2 at the mRNA level

and by FACS at the protein level. They exposed those cells to the NCP-CoV (2019-nCoV) spike protein. The authors disclosed that the ACE2 receptor and SARS-CoV-2 entry-facilitating transmembrane protease TMPRSS2 are expressed by all types of hematopoietic stem cells (5).

Likewise, Ropa et al. also explored the expression of ACE2 in primitive and mature blood cells using RT-qPCR as well as western blotting that ACE2 is expressed at both the mRNA and protein levels. Moreover, they established that the SARS-CoV-2 spike protein could induce critical cellular alterations in the primitive and mature hematopoietic cells (6). They also observed ACE2 expression on the cell surface of small subpopulations of mature blood immune cells, including 1-2% of T-cells, 2-4% of B-cells, and <1% of NK cells and monocytes. In their study, ACE2 receptor was found to be expressed in 15-60% of the HSCs, 5-50% of the multipotent progenitor cells and 5-15% multipotent lymphoid progenitor cells. The exposure to viral S protein critically affected those cell populations. CD34+ hematopoietic stem cells exhibited 33% less expansion, granulocyte-monocyte progenitors 38% less expansion, and common myeloid progenitors/megakaryocyte-erythroid progenitors 15-30% significantly less expansion when exposed to the SARS-CoV-2 S protein. Thus, SARS-CoV-2 S protein significantly impacts hematopoiesis and myeloid differentiation based on their findings (6).

The data on the implications regarding the viral attack on hematopoiesis and immune response in COVID-19 syndrome are accumulating. Ihlow and colleagues suggested that severe lymphocyte depletion and over-activation of the adaptive immune system commonly observed during the COVID-19 progression are caused by the substantial loss of B-cells associated with viral SARS-CoV-2 burden (24). The authors demonstrated BM hypercellularity with increased myeloid/erythroid ratio, and left shift of erythropoiesis with leukoerythroblastic anemia blood picture. Prothrombotic state is associated with left shift of BM megakaryopoiesis. Their striking finding is that CD20+ B-cell and plasma cell depletion in both BM and spleen of the patients with COVID-19 associated with severe lymphocytopenia. Interestingly, there was a tendency towards higher pulmonary SARS-CoV-2 RNA load in COVID-19 patients with B-cell depletion in their study (24). In accordance with these findings, a recent dual center study from Deutsche COVID-19 OMICS initiative demonstrated elevation of HLA-DRhiCD11chi inflammatory monocytes with an interferon-stimulated gene signature in mild COVID-19, and dysfunctional mature neutrophils, HLA-DRlo monocytes and occurrence of neutrophil precursors as evidence of emergency myelopoiesis in severe COVID-19 patients (25). Thus, severe COVID-19 infection is associated with profound alterations in the myeloid cell compartment providing a detailed insight into the systemic immune response to SARS-CoV-2 infection.

All of those preliminary data cast further focus on the interactions of pulmonary RAS and hematopoietic BM RAS for the proper description of the COVID-19 pathogenesis and clinical management in the bedside. SARS-CoV-2 entry and damage to human cells expressing ACE2 receptor is a key factor in determining the tropism and influencing the severity of infection. Therefore, following the respiratory tract illness by regulating molecular pathways associated with ACE2 receptor in the lungs, the virus might affect local BM RAS, as well. Subsequently, BM hematopoietic stem and progenitor cells can trigger the spreading of the virus to different circulating and local angiotensin systems including local adipose tissue RAS, local cardiac RAS, local pancreatic RAS and local renal RAS. That pathobiologic sequence could further enhance to a multi-systemic immune dysfunction.

The Intimate Relationship Between Local Pulmonary RAS and Bone Marrow RAS

While the BM is the major site of hematopoiesis in the adult, spleen and liver also has important hematopoietic functions in some part of life. Although all of these systems are well known in respect to their roles in hematopoiesis, accumulating evidence suggests that lung is also a primary site for platelet biogenesis and reservoir for resident megakaryocytes (MK) and HPCs (26,27). Lefrançais et al. (27) demonstrated that the lung contains an array of hematopoietic progenitors including short term-HSCs, multipotent progenitors (MPP)2, MPP3/4, and myeloerythroid progenitor populations, which were morphologically indistinguishable from BM primitive HPCs. These cells were found to exist at lower numbers versus the BM and spleen, except for larger short term-HSCs in the lung versus spleen. In accordance with these findings, studies also showed that thrombopoietin (Tpo) stimulation can cause platelet release in the pulmonary vasculature (28). Haznedaroglu et al. (29) explored local Tpo concentrations inside the pulmonary artery and associated vessels in patients with and without pulmonary hypertension (PHT). Tpo concentration inside the pulmonary artery was found to be significantly higher than the Tpo concentrations in the right and left ventricles in patients with PHT. Authors suggested that lung vasculature holding the major regulatory thrombopoietic hormone, Tpo, may be an important place for megakaryocytopoiesis. Based on those data it is reasonable to suggest that BM and lung tissue work in a harmony in hematopoiesis under the direct control of tissue RASs. Meanwhile, pulmonary inflammation is the key event in the lung damage of COVID-19

(30). Localized inflammation in the SARS-CoV-2+ patients can cause decrements in the anticoagulant pathways. Likewise, the inflammatory process leads to the stimulation of endothelial cells expressing tissue factor, secreting molecules. Those pathobiological pro-thrombotic events are driven by the monocytes, platelets, neutrophils, platelet-leukocyte aggregates, all of which are of hematopoietic BM origin.

Preventing immunogenomic progression of COVID-19 syndrome by disrupting pathobiological harmony between local pulmonary RAS and bone marrow RAS with RAS modulating agents

ACE2 catalyses the hydrolysis of angiotensin II to its metabolite, angiotensin 1–7 and angiotensin I to angiotensin 1–9 to protect tissues from several types of injuries (31). It is highly expressed in several human organs and tissues at varying degrees, including lungs (on the surface of type II alveolar epithelial cells), BM, heart (on myocardial cells, coronary vascular endothelial cells, and vascular smooth muscle), kidney (on proximal tubule cells), and small intestine (on the enterocytes) (10,32). Therefore, in addition to efforts to synthesize direct viral inhibitors of replication, using RAS modulating agents for preventing immunogenomic progression of COVID-19 syndrome may be a reasonable option for blocking ACE2 which is the cellular target of SARS-CoV-2 (12). In this context, RAS modulating drugs including soluble ACE2, angiotensin (1-7), TXA127 and MAS receptor agonists might be useful by not only blocking the entry of SARS-CoV-2 into the human cells, as well as by blocking the spreading of the virus from local pulmonary RAS to other local tissue RAS systems including BM.

Soluble ACE2 is a novel compound under development with two actions of mechanisms against SARS-CoV-2. The first mechanism is its capability to bind to viral spike protein and thereby neutralising SARS-CoV-2, and the second action of mechanism is minimising injury to multiple organs, including the lungs, kidneys, and heart, because of unabated RAS hyperactivation and increased angiotensin II concentrations (33,34). Inhibition of SARS-CoV-2 infections in engineered human tissues using soluble ACE2 was first demonstrated by Monteil et al. (35) in which authors showed that soluble ACE2 can significantly block early stages of SARS-CoV-2 infections and clinical-grade recombinant human ACE2 can reduce SARS-CoV-2 infection in cells and in multiple human organoid models. Apart from this experimental study, the safety and efficiency of soluble ACE2 was also provided in a patient with severe COVID-19. In this case report, intravenous delivery of soluble ACE2 demonstrated a significant effect on blocking the systemic spread of the virus from the lung to other organs (34). Angiotensin-(1-7) is another key component of the RAS, which can counter-regulate several deleterious effects caused by angiotensin II. Intravenous infusion of angiotensin 1-7 theoretically activate RAS axis to prevent a further drop in blood pressure and the ACE level will increase and the ACE2 level will decrease owing to the accumulation of angiotensin 1-7 (36,37). This means that providing high levels of angiotensin 1-7 and ACE while reducing inflammatory bradykinin will be protective against ACE2, the entry site of the virus into the host cells (38). The clinical potential of this peptide as a therapeutic agent to treat several pathologies including tumoral conditions by inhibiting the growth of tumor cells and reducing local inflammation and angiogenesis is successfully demonstrated (39,40). Thus, there are also ongoing clinical studies available investigating the safety, efficacy and clinical impact of the infusion of angiotensin-(1-7) in COVID-19 patients with or without respiratory failure requiring mechanical ventilation (www.clinicaltrials.gov; NCT04332666, NCT04401423, NCT04375124). Apart from angiotensin-(1-7), the identification of Mas as a G protein-coupled receptor for Ang-(1-7) undoubtedly contributed to establish Ang-(1-7) as a biologically active component of the RAS (41). Experimental and clinical evidences supported the idea that Mas receptor activation is an important mechanism to fight the deleterious effects triggered by an inappropriate increase in Ang II/AT1 receptor in different diseases as demonstrated by Santos et al. (42). Moreover, the activation of the Mas receptor with Mas analogs can be important additive measures to control the inflammatory response mediated by SARS-CoV-2 (43,44).

CONCLUSION

There is a body of evidence now that demonstrates the critical role of local tissue RAS systems in COVID-19 pathophysiology. Tissue-based RAS genes are important at the initiation of the infections caused by coronavirus family members and may have a strong relationship with the exchange of immune genes in due course following the infection (9). Thus, the spread of the disease to other parts of the body through RAS activation seems to be responsible for the progression of the disease from respiratory viral illness (SARS-CoV-2) to a multisystemic immunoinflammatory pro-thrombotic syndrome. Therefore, it is crucial to acquire a greater knowledge on the biological role of the tissue RASs within different organs and in distinct physiological pathways since the RAS components have the ability of widespread tissue involvement in COVID-19. Among them, the pathobiological interactions of the local pulmonary RAS and tissue-based hematopoietic BM microenvironment RAS together with their pharmacological manipulation seems to be the rational fields for future experimental and clinical research studies.

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