Endothelial cells are major players in SARS-CoV-2-related acute respiratory distress syndrome

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Commentary for "The fatal trajectory of pulmonary COVID-19 is driven by lobular ischemia and fibrotic remodeling".

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is probably the most consequential global public health threat. It has had a devastating global impact by overwhelming many healthcare systems in multiple countries and thus resulting in more than 6 million deaths worldwide as of October 4th 2022.[1] Despite improvements achieved by the vaccination campaign and the use of therapeutics, mortality among severe COVID-19 patients and chronic morbidity of severe COVID-19 survivors remain still high.

The spectrum of clinical manifestations of SARS-CoV-2 infection ranges from asymptomatic/mild signs to severe illness and mortality.[2] In particular, patients with greater severities display dyspnea, lymphocytopenia, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), or multi-organ dysfunction. The leading cause of mortality in COVID-19 patients is severe lung injury, caused by cytokine storm, coagulopathy, vascular injuries leading to macro and micro arterial, and venous thrombosis.[3–7]

Furthermore, long COVID-19 syndrome also involves persistent microvascular endotheliopathy associated with increased SARS-CoV-2 virions and/or its proteins in blood and tissues.[8]

As for classic ARDS, different pathological pathways have been described in COVID-19-related ARDS, among which a predominantly angiocentric inflammation with endothelialitis, microangiopathy, increasing prevalence of aberrant intussusceptive angiogenesis, and hypercoagulation associated with high prevalence of thrombi in the small arterioles and capillaries.[4,6] The direct role played by ECs in sustaining SARS-CoV-2-induced vascular dysfunction has been also proven *in vitro*.[9] SARS-CoV-2 does infect human primary lung microvascular ECs (HL-mECs), inducing release of pro-inflammatory and pro-angiogenic molecules which condition the microenvironment and stimulate not-infected HL-mECs to acquire an angiogenic phenotype.[9]

In a recent issue of *eBioMedicine*, Ackermann et al.[10] expanded the current mechanistic information on the fatal trajectory of pulmonary COVID-19 in order to elucidate the pathophysiology of the severe disease upon time, sort biomarkers to classify disease severity, and evaluate response to therapy. Ackermann et al.[10] analyzed autopsy specimens of patients who died from respiratory failure caused by severe COVID-19 in comparison to autopsy lungs from patients who died from pneumonia caused by severe influenza A (H1N1) virus infection, to lung explants obtained from patients with end-stage interstitial lung diseases (ILD), to uninfected healthy lung specimens. In addition, they analyzed plasma samples obtained from hospitalized COVID-19 patients, in comparison to samples obtained from hospitalized patients with influenza-related ARDS and to plasma samples from ILD patients. In this study, Ackermann et al.[10] highlight the utility of combining biological and molecular assessments to address a clinical issue. The analysis conducted by the authors demonstrates that the fatal course of COVID-19 advances with a peculiar morphological and molecular pattern. In particular, the results obtained suggest that fibrotic changes occurring in the lungs of COVID-19 patients are driven by secondary pulmonary lobular microischemia worsened by weakened bronchial circulation compensation which contributes to disease severity. Perturbation of microvascular circulation comprises irregular vascular lumens with numerous thrombi and evidence of endothelialitis. The authors also highlight the appearance of blood neo-vessel formation through intussusceptive angiogenesis, mostly due to vascular insufficiency and microischemia, which precedes fatal fibrotic remodeling of lung. Of note, intussusceptive angiogenesis was significantly higher in lungs of long-as compared to short-term hospitalized patients suggesting that longer hospitalization time may likely be associated with continuous microischemia phenomena.

These data were further corroborated by gene expression profiles and metabolomic analysis. Indeed, COVID-19 lungs displayed a higher expression of genes

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associated with angiogenesis and extracellular matrix formation. Interestingly, an increase in transcripts associated to fibrotic tissue remodeling was observed in contrast to a gradual decrease of those related to inflammation, epithelial–mesenchymal transition, and hypoxia. Of interest, the strong fibrogenesis observed during severe COVID-19 was also mirrored by elevated plasma levels of its related markers.

Altogether the findings reported by Ackerman et al.[10] demonstrate that the evolution of fibrotic morpho-molecular remodeling in COVID-19 is driven by secondary lobular microischemia and prolonged neo-vessel formation. The assessment of clinical and molecular characteristics of severe COVID-19 cases further highlights the unquestionable role of EC dysfunction in disease progression, thus uncovering novel insights on the topic, which may provide the basis for the future development of therapeutic strategies aimed to prevent COVID-19 dangerousness and lethality.

Contributors

Literature search, writing-original draft (F.C.), writing, review & editing (A.C.). All authors read and approved the final manuscript.

Declaration of interests

The authors declare no conflicts of interest.

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