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PHARMAPULSE

What is linking COVID-19 and endothelial dysfunction? Updates on nanomedicine and bioengineering from the 2020 AHA Scientific Sessions

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The outbreak of the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and declared as pandemic by the World Health Organization (WHO) on 11 March 2020, undoubtedly represents a global health threat worldwide.[1]

The 2020 Scientific Sessions of the American Heart Association (AHA) featured 139 presentations of works related to COVID-19. While most of the studies were reporting epidemiologic and clinical data from diverse regions of the world, some investigators focused on understanding the mechanisms of the disease, especially thromboembolism and cardiovascular complications. Indeed, we and others have linked the systemic manifestations of the disease to a direct or indirect involvement of the endothelium.[2–4] Notably, endothelial cells express all the co-factors necessary for the internalization of SARS-CoV-2 in human host cells (*Figure 1*). Our group has shown that the microRNA cargo of extracellular vesicles released by endothelial cells could contribute to the pathogenesis of thromboembolic complications of COVID-19.[5] On these grounds, we have selected some AHA presentations from experts in bioengineering and nanomedicine who developed innovative tools to dissect endothelial dysfunction in COVID-19.

Jason Hinman *et al.*[6] at UCLA generated 3D printed models of the human middle cerebral artery, endothelialized with human endothelial cells. Endothelialized models were subjected to 3D rotational perfusional culture at variable pulsatile flow rates and biotinylated recombinant Sars-CoV-2 S protein was used to judge regional vessel binding of virus. ACE2 expression was modulated in a flow-dependent manner. Pulsatile flow was able to drive ACE2 expression in these 3D endothelialized models and flow-mediated ACE2 expression was associated with binding of recombinant SARS-CoV-2 Spike protein to the vessel wall, thereby indicating a direct cerebrovascular susceptibility to SARS-CoV-2.[6]

Laura E. Niklason and her team at Yale developed an experimental platform that mimics physiological functions and cellular phenotypes of pulmonary vasculature, during homeostatic and diseased states.[7] To evaluate the ability of the engineered endothelium to modulate permeability in response to exogenous stimuli, lipopolysaccharide (LPS) was introduced to simulate acute lung injury; after LPS treatment, the pro-inflammatory signal was significantly increased and the vascular barrier was severely impaired in the repopulated lung. These results show that this novel platform recapitulates pulmonary microvascular functions and phenotypes at a whole organ level, which could be harnessed to study the pathophysiology of thromboembolism in COVID-19.

Some nanosized delivery systems, including liposomes and polymeric nanoparticles, have been recently approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for drug delivery in humans. These advanced carriers could be especially useful to address life-threatening human diseases and have been recently employed to deliver the mRNA-based COVID-19 vaccine.[8] Equally important, these techniques could be harnessed to elucidate the cellular and molecular mechanisms underlying the systemic manifestation of COVID-19. For instance, to study thrombosis in COVID-19, Tzung Hsiai *et al.* at UCLA developed liposome-nanoparticles exposing functional S-Spike to simulate the cell internalization route of SARS-CoV-2 and tested them in a microfluidic channel lined with human aortic endothelial cells.[9] This system offers the possibility to study thrombosis on a chip with the advantage of capturing the cellular responses on a rapid and small scale.

All the above-mentioned examples highlight the pivotal role of materials science in providing innovative technologies and exquisite tools for biomedical research and can be exploited to understand the molecular mechanisms underlying endothelial dysfunction in COVID-19, in order to identify and/or develop specific

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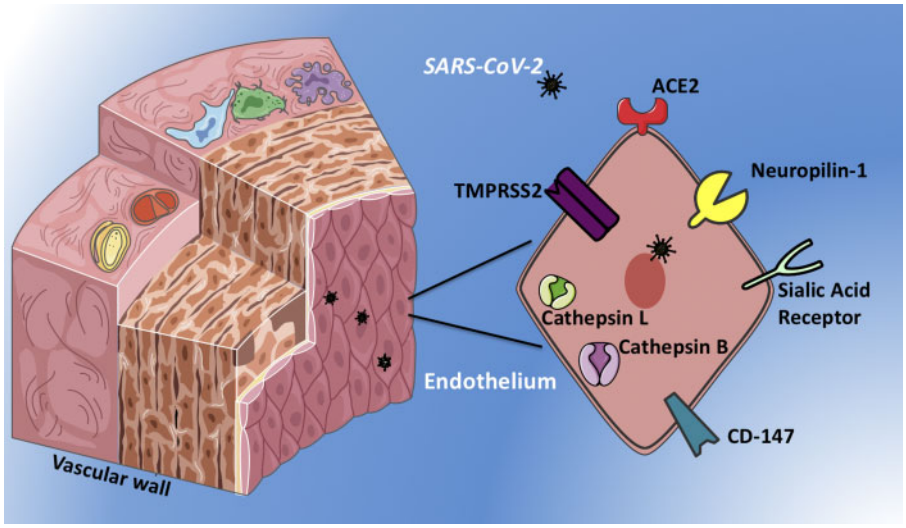

Figure 1 The main co-factors necessary for the internalization of SARS-CoV-2 in the host cell are expressed by the endothelial cell.

pharmaceutical approaches to tackle the systemic, and often fatal, cardiovascular and cerebrovascular complications of the disease.

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