SARS-CoV-2 and vascular dysfunction: a growing role for pericytes

Conor McQuaid, Axel Montagne

Centre for Clinical Brain Sciences, UK Dementia Research Institute at the University of Edinburgh, Edinburgh Medical School, Chancellor's Building, Edinburgh EH16 4SB, UK

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The editorial refers to ‘Preferential uptake of SARS-CoV-2 by pericytes potentiates vascular damage and permeability in an organoid model of the microvasculature’ by A.O. Khan et al., https://doi.org/10.1093/cvr/cvac097.

1. SARS-CoV-2 and the vasculature

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the viral cause of the COVID-19 global pandemic and was initially observed to act primarily on the respiratory tract. However, a growing body of evidence now suggests that SARS-CoV-2 affects multiple organ systems throughout the body (e.g. kidney, heart, liver, and brain, among others) and while endothelial inflammation and vasculopathy are common hallmarks within these affected organs, the underlying cellular and molecular mechanisms remain incompletely defined.

SARS-CoV-2 entry into a cell is essentially controlled by the binding of the receptor-binding domain (RBD) of the virus spike glycoprotein (Sp) onto the angiotensin-converting enzyme 2 (ACE2) receptor at the surface of the cell. SARS-CoV-2 also requires the transmembrane protease serine 2 (TMPRSS2) for Sp priming and complete cell entry. Importantly, ACE2, a key regulator of the renin–angiotensin system that is involved in cardiovascular function and blood pressure, is expressed on numerous cells of the vasculature, with a high level of expression found in pericytes originating from the lungs, heart, and brain.1–3 Thus, one may assume that if pericytes preferentially take up viral particles, this would trigger a detrimental cascade leading to their injury followed by vascular dysfunction, although this remains to be proven.

2. SARS-CoV-2 specially infects pericytes

In their recent study, Khan et al.3 sought to address this question and gain a better understanding of the role of perivascular pericytes in SARS-CoV-2 infection. The authors found that SARS-CoV-2 Sp localizes with NG2⁺ pericytes in post-mortem lung tissue of patients who died from COVID-19. In addition, they reported a possible detachment of pericytes as double positive NG2⁺/Sp⁺ pericytes do not line up with the pulmonary capillary endothelium. Interestingly, they also noticed an increase in intercellular adhesion molecule 1 endothelial expression at sites of high Sp level, emphasizing the importance of the pericyte–endothelium crosstalk in SARS-CoV-2 infection. They observed a decrease in endothelial barrier function as shown by a loss of VE-Cadherin expression, as well as an increase in prothrombotic von Willebrand factor and fibrin deposits within the COVID-19 pulmonary vasculature. These findings resemble those seen in the brain tissue of patients who died from COVID-19 with evidence of injured cerebral blood vessels accompanied with a dramatic increase in the extravasation of serum proteins, especially fibrinogen, indicating a disturbed blood–brain barrier.5,6 Of note, the vascular inflammation and hyperpermeability phenotype links in well with the increase in immune cell infiltration found in damaged tissue of COVID-19 patients and the highly detrimental ‘cytokine storm’.7

Khan et al. confirmed their clinical findings using a 3D vascular organoid model made of human induced pluripotent stem cells (iPSC)-derived endothelial cells, pericytes, fibroblasts, and other partially differentiated cells. First, they observed a preferential SARS-CoV-2 uptake by pericytes. Second, they revealed that Sp and the nucleocapsid protein (Np) induce pericyte death as well as impair endothelial integrity and survival, but contrary to the clinical data, without a significant activation of the endothelium. Third, they found that Sp and Np treatments lead to transcriptional changes of genes regulating vascular integrity.

Altogether, this article sheds light on the predominant role of pericytes in the SARS-CoV-2 pathophysiology and emphasizes the important and complex interactions between pericytes and endothelial cells in health and disease (Figure 1). The authors demonstrated that a pericyte-centric attack on the vasculature by SARS-CoV-2 could lead to downstream endothelial dysfunction rather than SARS-CoV-2 directly causing vascular damage by its interaction with the pulmonary endothelium. Remarkably, pericytes exposed to Sp were recently shown to undergo phenotypical changes associated with an elongated and contracted morphology accompanied with an enhanced expression of contractile and myofibrogenic proteins (e.g. α-smooth muscle actin, fibronectin, collagen-I),8 which can have dramatic consequences on vasomotion and blood flow regulation throughout the body. Both the dysregulation
of blood flow and endothelial activation can synergistically lead to vessel stalling as well as immune cell infiltration in COVID-19 affected organs. These would eventually trigger an over reactive immune response, which may cause long-term damage and/or death.

3. Current challenges and future perspectives

Although the preferential action of SARS-CoV-2 on pericytes has become clearer, several key questions remain to be resolved, including, but not limited to, the possible effects of Sp mutations, differing SARS-CoV-2 variants, and other possible receptors and surrounding vascular cells on the consequent vascular dysfunction.

SARS-CoV-2 is a homotrimer and each monomer contains two subunits (S1 and S2) with the S1 region containing the RBD, which recognizes and binds to the ACE2 receptor, while the S2 region mediates viral cell membrane fusion. Over the duration of the pandemic, mutations in the RBD of SARS-CoV-2 Sp have been reported in variants of concern and resulted in new waves of infections during the COVID-19 pandemic. Alpha, Beta, Gamma, and Omicron variants, which have numerous point mutations in the RBD of the Sp, have all shown increased transmission, increased severity, and reduced neutralization of antibody treatments. Some of these mutations, for instance N501Y and E484K, increase the uptake of SARS-CoV-2 Sp compared with wild type (WT) Sp in numerous cell types, including vascular cells. Interestingly, the use of antibodies blocking ACE2 in cultured human pericytes led to a partial reduction in the uptake of both WT Sp and Sp with the E484K or N501Y mutations, suggesting there are other receptors/pathways for SARS-CoV-2 Sp cellular uptake. Although controversial, CD147, an entry receptor for measles virus, has also been associated with the cellular uptake of SARS-CoV-2. CD147 is expressed in both endothelial cells and pericytes, and is up-regulated during inflammation and atherothrombosis.

With numerous new receptors being proposed, it highlights that other cells—that have either low or zero expression of ACE2 receptor—may be involved in the pathobiology of COVID-19. Indeed, pericytes are not
the only cells that are closely associated with blood vessels in the brain, the whole complex of the neurovascular unit is likely involved. For example, there is evidence that astrocytes wrapping around blood vessels could be another important target of SARS-CoV-2 in the brain. It was recently shown that SARS-CoV-2 can infect astrocytes via CD147 in primary and organoid cortical cultures, resulting in astrocyte reactivation and non-cell-autonomous neuronal death, which can lead to some of the neurological damage seen in severe COVID-19 cases.5

4. Conclusion
The recent literature is showing that COVID-19 infection is actually much more complex than initially thought and implicates a multi-system and multi-organ route of infection. Although progress is being made towards defining the exact mechanism of action of SARS-CoV-2, particularly at the vascular level, the understanding is far from complete. With the work of Khan et al., we are beginning to comprehend the extent of pericyte implication in SARS-CoV-2 infection and their role in catalyzing vascular dysfunction observed in some infected patients. Though more research is warranted, the possibility of targeting perivascular pericytes could prove a promising therapeutic avenue.

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