Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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See **Online** for appendix

Pulmonary intravascular coagulopathy in COVID-19 pneumonia

We read with pleasure the thoughtful Viewpoint by Dennis McGonagle and colleagues[1] on lung immunothrombosis during infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, some of the key pathogenetic events were not highlighted by the authors.

Evidence from the early stages of disease suggest the occurrence of diffuse alveolar damage with infiltrating multinucleated cells and few macrophages.[2] CT perfusion scans done in patients with early pneumonitis reveal microangiopathy that presents as hypoperfusion of the involved parenchyma (appendix). McGonagle and colleagues cite a study in which single-cell analysis showed no angiotensin-converting enzyme 2 (ACE2) expression in endothelial cells or alveolar macrophages.[1] However, other studies showed ACE2 expression in vascular endothelial cells in the lungs during infection with severe acute respiratory syndrome coronavirus (SARS-CoV),[3] or in the kidney during SARS-CoV-2 infection,[4] supporting the hypothesis that there is a receptor in all endothelial cells at the systemic level.

By infecting endothelial cells, the virus could alter the cells' function from the inside, as happens for other viruses. McGonagle and colleagues note that endothelial cells indeed express ACE2. The microangiopathy seen in patients with COVID-19 might therefore arise both from the inside (endothelial cells) and from the outside (platelets, cytokines, neutrophil extracellular traps, thrombophilic factors), resulting in, what we call endothelial leuko-thrombo-inflammation.

Alveolar haemorrhage can also occur in COVID-19 and an autopsy series from the USA showed foci of haemorrhage in all but one patient plus diffuse alveolar damage and mild-to-moderate infiltrates of CD4+ and CD8+ lymphocytes; CD4+ T cells were seen in aggregates around small blood vessels, some of which appeared to contain platelets and small thrombi. In addition, fibrin thrombi were present within the capillaries and small blood vessels with entrapment of numerous neutrophils. Neutrophil extracellular traps have been observed in the advanced phases of lung inflammation and one preprint paper reported the presence of CD61+ megakaryocytes.[5] Since platelets are normally produced in the lung, the thrombotic events are certainly facilitated. However, it is crucial to recall the hierarchical role of endothelial cells, which appear to be central regulators of the cytokine storm. In models of viral post-influenza inflammatory storms in the lung, triggering sphingosine-1-phosphate ($S1P_1$) receptors, which are expressed on endothelial cells and lymphocytes in the lung, suppressed cytokine production, innate immune cell recruitment, and cytokine release syndrome,[6] thereby decreasing lethality. Clinically, this finding could mean that, failing effective antiviral therapy (eg, remdesivir), treatments aimed at suppressing cellular aggregation or neutrophil extracellular trap formation and triggering $S1P_1$ signalling (eg, fingolimod) could be crucial in curtailing the endothelial leuko-thromboinflammatory storm before it starts, thus reducing the high mortality rate observed in patients with COVID-19 treated in intensive care units.

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We read with interest the Viewpoint by Dennis McGonagle and colleagues.[1] To account for unusual clinicopathological features of COVID-19 disease, particularly coagulopathy, the authors point to dysregulated immunity and systemic inflammation reminiscent of a cytokine storm or macrophage activation syndrome (MAS). Although the authors' contribution comes down firmly on the immunological side of the debate over whether COVID-19 coagulopathy is due principally to immune or endothelial dysfunction,[2] the common background assumption to both sides is that modelling COVID-19 using previously described clinical syndromes and traditional pharmacological and physiological mechanisms will lead to deeper insights into the disease.