Electron microscopy of SARS-CoV-2: a challenging task – Authors' reply

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Electron microscopy of SARS-CoV-2: a challenging task

Authors' reply

We thank Cynthia Goldsmith and colleagues for their interest in our recent Correspondence.[1] We described autopsy findings from patients who had died from COVID-19 and showed a systemic endotheliitis with evidence of loss of integrity of the endothelial monolayer.[1]

The framework of endotheliitis provides an explanation for the unique predilection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in those individuals with hypertension, diabetes, or established cardiovascular disease, a group known to have pre-existing endothelial dysfunction. COVID-19-endotheliitis could also explain impaired microcirculatory function across different organs and the frequently observed prothrombotic state with in-situ clot formation. Endothelial infection and injury by SARS-CoV-1 has been shown.[2] Our demonstration of viral particles using electron microscopy (EM) is supported by several reports independently describing ultrastructural round virus-like particles in the setting of a SARS-CoV-2 infection.[3-6] We demonstrated tubulo-reticular structures in the immediate vicinity of the spherical particles that are strikingly identical to SARS-CoV-1-associated membrane changes described by Goldsmith and colleagues in 2004.[7] In our EM thin-section images, the virus-like particles were relatively large (mean diameter 180 nm [SD 10]). However, subsequent analysis of more EM images has revealed a mean particle size of 67 nm (SD 15 nm, median 65 nm, 95% CI 41–102; n=33). Zhu and colleagues[5] noted that SARS-CoV-2 virions ranged from "about 60 to 140 nm". In another recent study,[6] virus-like particles in patients with confirmed SARS-CoV-2 infection were 70–110 nm in diameter. By comparison, SARS-CoV-1 viral particles analysed with the same technique (ultrathin EM imaging) were 50–80 nm in diameter.[7-10]

Goldsmith and colleagues have studied coronavirus isolates grown in cell culture, whereas our EM data of virus-like particles were obtained from a post-mortem kidney allograft obtained during autopsy. Since most other recent reports of patients with COVID-19 also describe postmortem findings, it remains unclear to what extent tissue type (cell culture, fresh biopsy material, or autopsy material), time to fixation, and postmortal autolysis alter subcellular structures in preparation for EM. This notwithstanding, these observed particles in patients with COVID-19 should be best designated as virus-like particles because definitive assignment of these structures as SARS-CoV-2 virions requires immuno-EM.

Investigations with vascular organoids that preceded our observations[1] showed that SARS-CoV-2 can infect human blood vessels via the ACE2 pathways, providing the first and direct evidence that the virus can indeed invade human vasculature.[11] Our findings have also been confirmed in descriptions of renal tropism of SARS-CoV-2, with detection of SARS-CoV-2 protein in human glomerular endothelial and epithelial cells.[12]

Importantly, our demonstration of virus cell infection in the kidney and endotheliitis[1] points to a general host inflammatory response causing hyperinflammation as a principal participant in the vascular pathology of COVID-19. Endothelial cell dysfunction, which might subsequently induce a prothrombotic state, could thus explain the vascular microcirculatory complications seen in different organs in patients with COVID-19.

We declare no competing interests.

*Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies Zinkernagel, Mandeep R Mehra, Felix Scholkmann, Reto Schüpbach, Frank Ruschitzka, *Holger Moch*

holger.moch@usz.ch

Department of Pathology and Molecular Pathology (ZV, MH, HM), Department of Cardiology, University Heart Center (AJF, FR), Institute for Intensive Care Medicine (PS, RA, RS), Division of Infectious Diseases (AZ), and Biomedical Optics Research Laboratory, Department of Neonatology (FS), University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland; and Department of Internal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (MRM)

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