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.

Cardiovascular Pathology 52 (2021) 107338

Contents lists available at ScienceDirect

Cardiovascular Pathology

journal homepage: www.elsevier.com/locate/carpath

Letters to the Editor

Electron microscopy identification of SARS-COV-2: what is the evidence? ☆,☆☆

To the Editor

Buja et al. review autopsy studies from COVID-19 decedents performed early in the pandemic and include their institutional experience of three autopsy cases [1]. This publication's electron microscopic images purportedly describe "viral particles within a vacuole in a renal glomerular endothelial cell" (Fig. 12B) and a "100-nanometer viral particle with nucleocapsid and membrane spike proteins free in the cytoplasm of a renal glomerular endothelial cell" (Fig 12C). However, Fig 12B shows a multivesicular body (MVB). MVBs are organelles of the late endosome type involved in the process of endocytosis, a cellular housekeeping mechanism that controls internal recycling and degradation processes by transport, sorting, and degradation of macromolecules. MVBs are characterized by multiple intraluminal vesicles (ILVs) of approximately 50-80 nm diameter contained within a round or oval-shaped limiting membrane measuring 250-1000 nm. Fusion of MVBs with lysosomes initiates the degradation of ILVs and their contents. Another fate of the MVBs is the release of ILVs into the extracellular space as exosomes upon fusion of the MVB limiting membrane with the cytoplasmic membrane.

In Figure 12C, the depicted structures are not in keeping with the characteristic replication cycle of coronavirus, which occurs within the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). New virions assemble by budding of the viral nucleocapsid into the ERGIC membranes forming vesicles (virions) on the *inside* of the ERGIC vacuole; they do not form *de novo* free in the cytoplasm. These virions are subsequently released to the extracellular space by fusion of the vacuoles with the host cell's cytoplasmic membrane [2,3]. Therefore, the virions are always membrane-bound within the cytoplasm of the host.

Based on these observations, the images portrayed by Buja et al., are not definitively supportive of SARS-Cov-2 infection but rather represent subcellular structures misidentified as virions. Similar highly contested reports have emerged in the recent COVID-19 literature, eliciting a series of publications refuting these findings, reviewed by Bullock et al. [3].

In summary, diagnostic EM represents a powerful and valuable tool for identification of viral structures. However, careful consideration should be given to viral biology and morphogenesis, artifacts of delayed postmortem fixation, lack of detection due to possible viral clearing, and sensitivity of the methodology. A collaborative effort amongst pathologists, microbiologists and electron microscopists trained in recognizing viral structures is paramount to further our current understanding of SARS-COV-2 biology.

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☆ Financial disclosure: None to report.
☆☆ Conflicts of interest: None to report.

https://doi.org/10.1016/j.carpath.2021.107338