Where does SARS-CoV-2 go to in man?

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†Invited Commentary for Gray-Rodriguez et al. Multisystem screening reveals SARS-CoV-2 in neurons of the myenteric plexus and in megakaryocytes. J Pathol 2022; 257: 198–217.

Abstract

SARS-CoV-2 virus, the cause of COVID-19 disease, establishes infection in the human body via interaction with the angiotensin-converting enzyme 2 (ACE2) receptor on cell membranes. The lung is the major organ affected, and all respiratory epithelium from nose to alveolus is infectable. A recent study published in The Journal of Pathology looked at a wide range of other human tissues, mostly autopsy-derived, to identify susceptible cells. The virus (associated with ACE2) is found in all endothelial cells (an important finding), renal and biliary epithelium, in megakaryocytes, and occasionally in hepatocytes. It was not found in heart myoﬁbres or brain neurones but is present in gut myenteric plexus cells. This work conﬁrms previous work on SARS-CoV-2-infectable cells, and so supports investigations into the pathogenesis of COVID-19 disease as it affects (or does not directly affect) the different organs.

Keywords: SARS-CoV-2; COVID-19; pathology; virus location; heart; autopsy

Received 25 July 2022; Accepted 19 August 2022

No conﬂicts of interest were declared.

Since early 2020, pathologists have been examining the bodies of patients who die of or with SARS-CoV-2, the virus causing COVID-19 disease. This infection has its major effects in the lung, causing an acute lung injury syndrome that resolves or progresses to organising pneumonia and, often, death. In addition, it was soon noted that small and large blood vessels were often thrombosed, followed by the appreciation that the disease involved a systemic thrombophilia. Over the last 2 years of research (the COVID-19 publication count has nearly reached the total for that of HIV/AIDS over the past 40 years), numerous additional syndromes have been associated with SARS-CoV-2 infection including – with greater or lesser conﬁdence – anosmia, gastrointestinal upsets, encephalitis, myocarditis, glomerular disease, vasculitis, pancreatitis, increased stillbirth rates, T-cell depletion, and macrophage activation in the lympho-reticular system. Knowing which tissues and cells actively take up the virus and what happens thereafter at the cellular level would contribute to unravelling the correct range of true SARS-CoV-2-related disease.

We know that SARS-CoV-2 is an enveloped RNA virus, whose surface spike (S) protein binds to target cell receptors, particularly the angiotensin-converting enzyme 2 (ACE2) receptor. There is cleavage of the S protein by cell proteases such as TMRPRSS2, and fusion of viral and cell membranes. Multiple tissues express ACE2, as they do TMRPRSS2, but what tissues express both and can thus effect entry and cytopathic damage by the virus?

The study by Gray-Rodriguez et al in a recent issue of The Journal of Pathology [1] is a multi-centre examination of autopsy tissues in COVID-19 deaths, and some biopsies, involving several medical schools, the Institute of Neurology in London, and the National Infection Service, United Kingdom Health Security Agency, at Porton Down. We have here a comprehensive survey of human tissues from patients dying with proven SARS-CoV-2 infection and known chronologies of disease, compared with pre-COVID control patients. Importantly, these studies precede the introduction of vaccines against SARS-CoV-2.

Tissue analysis utilised formalin-ﬁxed, parafﬁn-embedded immunohistochemistry with a mouse anti-SARS-CoV-2 nucleocapsid protein monoclonal antibody; mock-infected cell pellets were created for positive/negative controls. Also, hamsters infected with SARS-CoV-2 were studied at autopsy.

The results showed in human tissues that SARS-CoV-2 is present in endothelial cells in all organs: in nasal, respiratory, renal, and biliary epithelial cells, and also in megakaryocytes. It was not found in brain neurones or glial cells, nor in heart myoﬁbres, and only occasionally in hepatocytes.

The controversial status of myocarditis in COVID-19 disease – is it a true myocarditis as pathologists deﬁne it,
or a borderline (interstitial) myocarditis representing systemic inflammation without direct myofibre involvement? – is partially resolved by not finding the virus in heart muscle cells (Figure 1, left panel). My personal belief is that the usual COVID-19 disease does not involve a true myocarditis. Borderline myocarditis is encountered in the uncommon post-infectious multisystem inflammatory syndromes in children and adults (MIS-C and MIS-A, respectively [2]); and a true myocarditis occurs rarely as a reaction to some COVID-19 vaccines, but that pathogenesis is a completely different, immunological phenomenon.

Co-location of SARS-CoV-2 with the ACE2 receptor was also demonstrated. Unexpectedly, the virus was also located in the gut myenteric plexus and ganglion cells.

Chronologically, the presence of SARS-CoV-2 in lung tissues is always associated with extrapulmonary viral presence. The concept that extrapulmonary dissemination of infection is haematogenous, primarily from the lungs, gains credence from other clinico-pathological observations: the thrombophilic phenotype in COVID-19 disease only happens in patients who have the lung disease, not in those who are merely nasal swab-positive but who at autopsy are found to have normal lungs. The SARS-CoV-2 infection of megakaryocytes might also impact on the thrombophilia process, although it seems more probable that infection of the critical endothelium is more important in this regard.

The universal infectability of endothelial cells, and possible persistent infection of the critical vascular networks in organs such as the brain and heart, may well have a bearing on the pathogenesis of the 'long COVID' syndrome [3]. Since there are no autopsy studies of long COVID-19 (as yet), this could be a reasonable basis for further in vivo investigations.

The authors speculate on the significance of finding SARS-CoV-2 in the gut myenteric neuronal plexus (Figure 1, right panel), in contrast to its absence in the brain. (This latter datum is congruent with the neuropathological consensus that there is no standard encephalitis, i.e. CD8+ T-cell parenchymal and perivascular infiltration, in COVID-19 disease.) Digestive symptoms – diarrhoea and abdominal pain – are consistent with such infection. But whether, as the authors speculate, there is a general link between the development of neurodegenerative diseases such as Parkinson’s disease and gut neurone pathology may be a little premature.

Overall, it is useful to have a well-illustrated, and well-controlled, display of where SARS-CoV-2 is found at the cellular level in the human body. This information will be used in future investigations into the pathogenesis of the several COVID-19-related disease syndromes.

References
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