Reservoirs of SARS-CoV-2 and their potential role in Long COVID

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A review article in *Nature Immunology* summarizes what is currently known about the persistence of SARS-CoV-2 virus in the body after COVID-19. Theorized as a possible cause of Long COVID, the ongoing presence of the virus could trigger immune responses that account for most or all the sequelae of COVID-19. For the virus to persist, a "reservoir"—that is, a particular tissue that is host to either viral genetic material or ongoing viral replication—must exist.

The authors noted that viruses similar to SARS-CoV-2 persist in the body after infection and cause chronic illnesses as a direct result. The genetic material of the SARS-CoV-2 virus is RNA, and in particular it is single-stranded RNA or "ssRNA" for short. Several other ssRNA viruses—including Zika virus, Ebola virus, enteroviruses, and the measles virus—are known to persist in tissues for months to years after initial infection.

The persistence of these other ssRNA viruses often results in chronic disorders including heart, eye, neurological, and musculoskeletal syndromes. Therefore it is a reasonable hypothesis that SARS-CoV-2 exhibits similar behavior that is responsible for at least a significant proportion of cases of Long COVID. It should also be noted that reservoirs of these viruses have been associated with viral mutations while the virus replicates for long periods of time in the body as well as ongoing transmission of the virus—often silent given that individuals are often months past acute infection.

The purpose of the review article was to assess what science currently has discovered about reservoirs of SARS-CoV-2 and their association with Long COVID. Also, the authors reviewed the possible biological mechanisms by which viral reservoirs might result in the broad array of sequelae seen in Long COVID patients.

The answer is that dozens of tissues are documented reservoirs of SARS-CoV-2 for periods up to 676 days (nearly two years). Viral RNA and associated proteins have been found in brain, nerve, gastrointestinal tract, lymph node, lung and breast tissue, among others. Viral RNA and proteins, including the spike protein, have been found circulating in blood plasma for over a year post-infection.

The reason why so many tissues serve as reservoir of the virus is still a subject for future study. One leading hypothesis is that most human tissues are dense with Angiotensin Converting Enzyme 2 (ACE2) receptors, and ACE2 receptors are the primary way the SARS-CoV-2 virus binds cells in order to enter them. Notably, ACE2 receptors are particularly abundant in the tissues of the gastrointestinal tract, brain, lung, heart and blood vessels.

The research also demonstrates that individuals with viral reservoirs test negative for the virus by testing of nasopharyngeal (nose and throat) or blood specimens, or in some studies, both. This fact is important, to demonstrate that ongoing primary infection is not confounding the findings, and that these tissues are in fact serving as viral reservoirs post-infection.

The evidence that viral reservoirs are associated with Long COVID is less strong, but nevertheless highly suggestive. As the virus persists in various tissues, viral proteins—including the spike protein—"leak" out into circulating blood plasma. Studies of Long COVID patients have demonstrated persistence of the S1 protein in up to 64 percent of Long COVID patients vs. only 35 percent of control patients who recovered. The results for spike protein are more dramatic, persisting in 60 percent of Long COVID patients vs. zero control patients in one study.

The evidence for both viral reservoirs and their association with Long COVID also comes from studies looking at T cells, a type of white blood cell involved in fighting infection. T cells that are specific to a virus rapidly multiply when that virus is present in the body and then drop off in numbers after the infection. Thus, the

persistent elevation in numbers of SARS-CoV-2 specific T cells is evidence that the virus is still present in significant quantity in the body.

First, individuals with the presence of viral RNA and proteins in tissues have been found to also have high numbers of SARS-CoV-2 T cells. These results confirm that SARS-CoV-2 is not an exception to the rule: when the virus is present, so are virus-specific T cells.

Second, the persistent elevation of SARS-CoV-2 specific T cells has been found in Long COVID patients. One study found that these levels were 6 to 105 times higher in Long COVID patients than in controls. Another study showed that the SARS-CoV-2 T cells had markers that indicated recent T cell activation and/or exhaustion, consistent with active immune response to the presence of virus.

The review also looked at the hypothesized mechanisms by which viral reservoirs result in the broad constellation of phenomena seen in Long COVID patients. The prolonged presence of the virus may directly damage tissues and/or induce prolonged inflammatory responses that damage tissues progressively over time. Also, it is known that viral proteins disrupt the body's feedback loops that regulate metabolism, gene expression and immune responses. Another hypothesis posits that the virus directly induces clot formation that causes damaging inflammatory responses.

Specific mechanisms called out by the authors for special consideration include effects on the the vagus nerve, induction of autoimmune responses, and the neurological system.

Infection with SARS-CoV-2 has been associated with disruption of the microbiome, or the set of all bacteria living in the body and most especially the gastrointestinal tract. The kinds of disruptions seen are known from prior research to be associated with the development of certain conditions, including those seen in Long COVID. In particular, it could be an important factor in life-threatening after-effects of COVID-19 seen in children, called Multisystem Inflammatory Syndrome of Children or MIS-C.

The vagus nerve has tens of thousands of branches that supply nervous energy to all the major organs in the trunk of the body. Activation of this nerve is associated with numerous non-specific symptoms, and most of these symptoms have been described in Long COVID patients. They include fatigue, difficulty concentrating, anxiety, depression, and muscle and joint pain. Either direct infection of the nerve—which has been found post-infection—or activation of its branches by immune responses in the tissues they stimulate, could explain the common occurrence of these non-specific symptoms in Long COVID.

With respect to autoimmunity, research has found that the antibody response to SARS-CoV-2 infection often includes induction of antibodies that attack the patient's own tissues. Similar types of autoimmunity have been seen in Epstein-Barr Virus (EBV) infection. Some work has hypothesized that SARS-CoV-2 infection reactivates latent EBV in the body. Whether the autoimmunity is thus directly induced or indirectly through EBV reactivation or both is not known.

Direct infection of the central nervous system (CNS) and ongoing inflammatory responses to the virus in CNS tissues might explain the increased risk for developing Alzheimer's disease in COVID-19 sufferers. One study found increased deposition of protein amyloid-beta (A beta) in brain tissues obtained from hospitalized patients severely ill from COVID-19. A beta has been found in plaques in Alzheimer's patients and seems to have an antimicrobial role generally against viruses and bacteria.

The review article concludes with an extensive list of 16 "major areas of opportunity" for future research into SARS-CoV-2 reservoirs and their impact on Long COVID. Despite the promising and important research conducted to date, the scientific community still has far to go to clarify our understanding of Long COVID and develop effective treatments for it.

The article thus highlights the stark impact of the ruling class's criminal indifference to the pandemic and its long-term consequences. Reservoirs of the SARS-CoV-2 virus are associated with extraordinary long-term morbidity and mortality that could have been avoided with a policy of eradication of the virus. Reservoirs also cannot be ruled out as sources of ongoing transmission and development of new variants of the virus, both of which prolong the pandemic and its effects.