Groundbreaking study uncovers mechanism of blood clotting caused by COVID-19, points to possible treatments

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8 September 2024

One of the hallmarks of COVID-19, the disease caused by SARS-CoV-2, is a multi-organ system process characterized by the formation of blood clots in small vessels. What was most puzzling in the early days of the COVID-19 pandemic were the unusual blood clots and strokes found among patients, even in those who were asymptomatic and irrespective of age. Most unusual had been that these COVID-induced blood clots were resistant to degradation despite adequate anticoagulation therapy.

A groundbreaking study conducted by the Gladstone Institutes and recently published in the journal *Nature* has uncovered the mechanism of these processes that lead to substantial tissue and organ damage, including in the brain, lungs, heart, and kidneys, as well as viral persistence and Long COVID. The authors write:

> The prevalence and severity of coagulopathy [blood clotting] and its correlation with the immune response and neurological complications in Long COVID suggest as yet unknown mechanism of COVID-19 pathogenesis.

With respect to the pathological blood clotting disorder common in COVID-19 patients, they explain:

> Hypercoagulability in COVID-19 is associated with extensive fibrin deposition in inflamed lung and brain. Fibrin is derived from the soluble blood protein fibrinogen after activation of coagulation and forms the central structural component of blood clots.
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> Fibrin is deposited at sites of vascular damage or blood–brain barrier (BBB) disruption and is a key proinflammatory and prooxidant activator of the innate immune response in autoimmune, inflammatory and neurodegenerative diseases. Neurovascular injury and reactive microglia are detected at sites of parenchymal fibrin deposition in brains of patients with COVID-19.
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> BBB disruption correlates with brain fog in long COVID, and increased plasma fibrinogen is a predictive biomarker of cognitive deficits after COVID-19. However, the role of blood clots in COVID-19 inflammation and neurological changes remains largely unclear, and therapies to combat their effects are not readily available.

With more than 400 million people the world over estimated to be suffering from symptomatic Long COVID, and essentially everyone having already been infected three to four times on average, identifying this crucial primary mechanism in the disease and possibly developing treatments for this unmet need is of the highest urgency.

Tendency to form blood clots is well understood as part of inflammatory pathways. Specifically, under conditions of homeostasis, the tendency to form clots is balanced by inhibitory pathways. However, when inflammation is encountered, such as in tissue damage and injury, the clotting cascades that recruit cells and molecules to form clots and stop bleeding are initiated.

In COVID, these processes are over expressed and until recently were thought to be a byproduct of the immune response to the invading virus that led to a severe inflammatory response known as a cytokine storm.

However, the researchers discovered that a key protein in the clotting cascade, known as fibrin, is directly responsible for the toxic inflammatory effects of COVID. As the study found, fibrin becomes more toxic in COVID as it binds to the virus and immune cells, leading to unusual clots and fibrosis which cause inflammation. The discovery also underscores the possibility that new treatments can be designed to address the main problems caused by SARS-CoV-2.

As the senior investigator at Gladstone and the director of the Center for Neurovascular Brain Immunology at UC San Francisco, Dr. Katerina Akassoglou, noted, “Knowing that fibrin is the instigator of inflammation and neurological symptoms, we can build a new path forward for treating the disease at the root. In our experiments in mice, neutralizing blood toxicity with fibrin antibody therapy can protect the brain and body after COVID infection.”

Co-investigator, virologist and director emeritus at Gladstone, Dr. Warner Greene, added, “We know of many other viruses that unleash a similar cytokine storm in response to infection, but without causing blood clotting activity like we see with COVID.”

Prior to this study, scientists and researchers had thought that the blood clots associated with COVID were a byproduct of the immune response against the virus that led to a super-charged inflammatory state.

Akassoglou and her group felt such explanations were not correct. She explained, “We began to wonder if blood clots played a principal role in COVID—if this virus evolved in a way to hijack clotting for its own benefit.” And this proved correct.

What the researchers found in their experiments using mice was that fibrin bound directly to the virus spike protein, leading to unusual blood clots that demonstrated enhanced inflammatory activity. To confirm this finding, they then genetically reengineered the mice such that it blocked the fibrin’s inflammatory properties without altering the protein’s critical blood clotting abilities.

An accompaniment review from the Gladstone Institutes to the *Nature* report notes:

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> When mice were genetically altered to carry the mutant fibrin or had no fibrin in their bloodstream, the scientists found that inflammation, oxidative stress, fibrosis, and clotting in the lungs didn't occur or were much reduced after COVID-19 infection.

Somewhat paradoxically, the researchers also recognized that although fibrin activates many white blood cells to cause inflammation, it conversely suppresses the activity of a type of immune cell called natural killer (NK), which normally work to destroy viruses in the body. In mice where fibrin had been depleted, the NK cells functioned to eradicate the SARS-CoV-2 viruses. The authors wrote:

> These findings indicate that fibrinogen is required for SARS-CoV-2 infection in the lung and pulmonary lesion formation through inflammatory activation and suppression of viral clearance involving NK cells.

With respect to neurological manifestations of COVID infections, including the ubiquitous "brain fog," and which scientists believe can trigger neurological diseases such as Alzheimer's and multiple sclerosis, the Gladstone Institutes team showed that fibrin was responsible for the pathologic activation of the brain's immune cells known as microglia that led to the degeneration of the neurons.

The autopsy of infected mice demonstrated fibrin together with toxic microglia. However, when fibrin was inhibited, inflammation in the mice brains was significantly reduced. In the discussion section of their study, they remarked:

> Increased BBB [*Blood Brain Barrier*] permeability associated with parenchymal fibrin deposition is a feature of COVID-19 neuropathology. In the brain of some patients with COVID-19, detection of spike and viral RNA suggests potential neuroinvasion. Our data and previous literature support that, while spike can enhance fibrin toxicity, even in the absence of spike, fibrin is deleterious in diseases such as multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, colitis and periodonditis. Thus, fibrin may be deposited either together with spike when spike is present in the brain or through an open BBB after peripheral infection without neuroinvasion or spike coupling.

After elucidating how fibrin leads to tissue injury after COVID infection—activating a chronic form of inflammation and by suppressing a beneficial NK cell response capable of clearing virally infected cells—the authors speculate that if these negative consequences could be neutralized, this may resolve the severe symptoms seen with COVID and prevent or mitigate Long COVID.

In support of these hypotheses and potentially developing a new treatment against severe COVID and Long COVID, Dr. Akassoglou's lab employed a monoclonal antibody they had previously developed that targeted fibrin called 5B8, which protected against neuronal inflammation and degeneration. This immune therapy was injected in mice either before SARS-CoV-2 infection or 24-hours after. They also tested it in a mouse-model infected with the Delta variant known for high neurological involvement and associated with greater risk of Long COVID.

In all instances, mice receiving immune therapy with 5B8 were found to suppress SARS-CoV-2 pathogenesis. The brain of immune-treated mice infected with the Delta variant demonstrated "decreased microglial reactivity and white-matter injury compared to… controls. In infected mice, 5B8 reduced the loss of cortical neurons… a feature of severe COVID-19 brain pathology associated with microglial nodules and neurovascular injury." Inflammation was suppressed and increased neuronal survival was observed. Notably, 5B8 does not increase bleeding.

Given these successes, Gladstone Institutes reported that 5B8 is already in phase one safety and tolerability clinical trials to assess how humans will react to the new treatment before proceeding with more advanced trials in COVID and Long COVID patients. In support of these developments, Greene said, "The fibrin immunotherapy can be tested as part of a multipronged approach, along with prevention and vaccination, to reduce adverse health outcomes from Long COVID."

Importantly, the authors underscored the fact that the anti-COVID vaccines that utilize portions of the spike protein do not elicit the fibrin-inflammatory response seen with infections. They note that a study of 99 million vaccinated individuals led by the Global COVID Vaccine Safety (GCoVS) project found no excessive clotting or hematologic disorders that met any of their prespecified thresholds for safety. On the contrary, the vaccines ameliorated and protected individuals from clotting complications caused by COVID.

The findings of the present study are a pivotal moment in the elucidation of the pathology caused by COVID-19, especially under the now universal policy of "forever COVID," in which mass infection has been normalized at great detriment to the world's population. The fact that a potential treatment exists that can be used to prevent or mitigate the dreaded manifestations of this dangerous virus is a boon for humanity.

However, and assuredly, because of the nature of capitalism, any success in this realm will mean these therapeutics will be chained to the profit motive of the healthcare and pharmaceutical industries, leaving billions of people across the globe without recourse, as witnessed by the rabid vaccine nationalism which emanated from the imperialist powers when the mRNA anti-COVID vaccines were first introduced.

In order for such scientific breakthroughs to translate into genuine progress for all of humanity, society must be reorganized on the basis of socialist principles, in which social needs take precedence over private profit.

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