Cause of long COVID remains most troublesome question about the syndrome

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What causes long COVID? More than three years after the start of the pandemic, this remains the most bedeviling question about a mystifying syndrome estimated to affect some 65 million people globally—an

epidemic in its own right with no clear end in sight.

Long COVID presents with remarkable variation across individuals. It can involve different organs and organ systems and different degrees of severity. One thing is becoming increasingly clear: the condition is likely to have long-lasting physiologic, social, and economic consequences, ripple effects of the initial disaster.

By some accounts, more than 1 million people in the United States alone may be pushed out of the labor force because of long COVID, causing both individual financial devastation and hurting the economy as a whole. This calculus does not factor in the sheer human toll of the disease.

Although infection with SARS-CoV-2 is the known spark plug that ignites long COVID, no one yet knows how this syndrome arises at the cellular and molecular levels. The answer holds the key to solving the long COVID puzzle. It may also help scientists understand syndromes that resemble long COVID and can develop in the wake of other acute infections, such as Lyme disease or herpes zoster.

Without a clear understanding of the driving mechanism—the fuel causing and sustaining the fire—long COVID treatment will remain confined to alleviating symptoms rather than resolving the underlying problem.

To be sure, in the last three years, researchers have gleaned some important insights about long COVID. They have defined the clinical syndrome and the organ systems involved; they have characterized how often it occurs and how widespread it is; and they have identified some of the key risk factors.

But for now, researchers are still circling the periphery of the terra

incognita that is the cause of long COVID.

With accumulating evidence, several hypotheses have emerged that are bringing scientists closer the answer.

Not a single disease

The range of symptoms is baffling: fatigue, malaise, heart palpitations, blood clots, hair loss, persistent cough, loss of lung function, muscle pain and joint aches, brain fog, headache, depression, anxiety, sleep disturbances, loss of smell, and gastrointestinal problems.

These clinical manifestations point to multiple mechanisms—so much so that researchers are beginning to view long COVID not as a single disease but as multiple disease subtypes, even if instigated by the same virus.

However, symptoms by themselves are unreliable indicators of underlying mechanisms. This underscores the importance of getting deep into the molecular roots of dysfunction. Defining these disease subtypes matters beyond mere classification.

"Physiologic perturbations are often the result of many intersecting pathways," said Bruce Levy, the Parker B. Francis Professor of Medicine at Harvard Medical School and an investigator at the HMS-led Massachusetts Consortium on Pathogen Readiness.

"These perturbations could be exquisitely defined clinically, but underlying the presentation may be very different mechanisms," added Levy, who is also interim chair of the Department of Medicine and chief of the Division of Pulmonary and Critical Care Medicine at Brigham and Women's Hospital.

For example, recurrent blood clots, fatigue, decreased exercise tolerance, and compromised lung function could all arise from ongoing low-grade inflammation. However, this chronic inflammation can be fueled by several distinct pathways—low levels of circulating virus, reactivation of dormant infections, immune dysfunction, and more. Each pathway will demand a different treatment.

"I think that we're going to find that there are these sub-phenotypes with distinct driving mechanisms, and they're just so pivotal to understand because they'll impact our treatment in really important ways," Levy said. "Let's say one of these phenotypes relates to viral persistence and another relates to autoimmunity. You might not want to suppress the immune system in somebody who has viral persistence, but in somebody who's got an autoimmune mechanism, you may want to do this."

Here are the hypotheses about long COVID mechanisms that scientists are converging upon:

- Viral persistence, marked by ongoing SARS-CoV-2 shedding, likely causing the virus to continuously provoke the immune system, which, in turn, leads to chronic inflammation. One study found persistent viral RNA in the feces of a subset of individuals months after clearing the original infection. These individuals also reported lingering GI symptoms months after COVID diagnosis. Another study found spike protein continuously circulating in the plasma of people with long COVID.
- Reactivation of dormant chronic infections. Reactivation of Epstein-Barr virus, EBV, which causes mononucleosis, is a prime suspect in some patients with long COVID. Research shows that EBV antibody levels are correlated with persistent long COVID symptoms. Unpublished work by MassCPR researcher Jennifer Snyder-Cappione and colleagues shows that the memory T cell response specific to EBV rises dramatically over time in the

months following COVID-19 diagnosis in many long COVID patients but not in fully recovered individuals. Other dormant viruses awakened by infection with SARS-CoV-2 could also drive disease development in some individuals.

- Dysregulation of the gut. Studies have found that after SARS-CoV-2 infection, some individuals develop a condition in which tight junctions—molecular channels in the gut—get looser and leakier, allowing gut microbes to seep into the bloodstream and leading to immune activation and chronic inflammation. This condition is marked by high levels of the protein zonulin, which regulates tight-junction permeability.
- Microclot formation and platelet dysfunction. The formation and long-term presence of tiny clots in the cells that line blood vessels and organs may fuel long COVID symptoms in a subset of cases. These microclots may, in turn, ignite inflammatory responses, researchers say, leading directly and indirectly to persistent fatigue and exhaustion, two of the most commonly reported symptoms of long COVID.
- Classic autoimmunity. In some people, SARS-CoV-2 infection can trigger autoimmune conditions that can lead to symptoms associated with long COVID. One analysis showed that individuals with long COVID have increased rates of autoimmune diseases, such as rheumatoid arthritis and lupus, following SARS-CoV-2 infection. That an acute infection can ignite autoimmune conditions in susceptible individuals is not a novel concept, but the pandemic offers new insights about this phenomenon. Complicating the picture is that not all people with autoantibodies have clinically diagnosable autoimmune conditions. Researchers also note that it is possible in some people that long COVID may unmask preexisting autoimmune diseases that remained subclinical before the infection.
- Gut microbiome disruption. Research suggests that depletion of certain anti-inflammatory gut bacteria during and immediately

following SARS-CoV-2 infection may result in lingering inflammation and contribute to the development of long-term symptoms of long COVID.

- Direct damage by the virus. SARS-CoV-2 itself, rather than the host's defense against it, inflicts damage directly by altering cells and tissues to cause ongoing symptoms. For example, a study led by HMS found that olfactory cells that line the nasal passages may be the primary target for this viral assault, causing long-lasting anosmia, or loss of smell. The virus may also cause damage to heart muscle cells, a condition known as myocarditis, and lead to inflammation of the tissue that envelops the heart, a condition called pericarditis. SARS-CoV-2 can also injure the kidneys and destroy lung cells. While the effects of the viral assault can dissipate over time, a subset of patients may never achieve full recovery.
- Persistent immunologic dysfunction. A number of studies have found evidence of immunologic dysfunction—marked by alterations in immune cells and proteins—for months following SARS-CoV-2 infection in people who report long COVID symptoms. Researchers, however, note that it is possible these immune changes may be mere bystanders to the actual underlying mechanisms that fuel long COVID. If so, treating such "red herring" indicators may not necessarily lead to clinical benefit and might even cause harm. Thus, Levy and Snyder-Cappione say it would be critical to link cellular and molecular changes directly with actual long COVID symptoms.

Understanding the basic mechanisms—what is happening at the levels of cells and molecules—can shed light on what patients are experiencing and, more importantly, why they are experiencing specific symptoms.

Understanding the why can inform the how. How to design reliable diagnostic tools and treatments that alleviate and even prevent the

condition. Understanding the underlying mechanisms can also help researchers define the most reliable biomarkers —biological signals or footprints—to help track how the disease is progressing and responding to treatment. For example, in people whose symptoms are caused by microclots, certain blood tests could help determine who is responding to treatment with anticlotting medications.

Defining the basic biology of long COVID can also help scientists understand better other conditions like it that affect millions of individuals globally.

Vaguely familiar

SARS-CoV-2, the viral instigator of long COVID, is a novel pathogen, but long COVID shares characteristics with other conditions that develop after an acute infection. These include postinfectious syndromes following infections with the viruses that cause Ebola, dengue, polio, chikungunya, influenza, and certain herpes viruses, as well as nonviral pathogens such as Borrelia, one of the organisms that causes Lyme disease.

This resemblance was one of the first things that caught the attention of many researchers studying long COVID.

"I was surprised by the strikingly common cluster of distinct symptoms present in some of the most severe forms of long COVID and other postinfectious disease syndromes," said immunologist Snyder-Cappione, assistant professor in the Department of Virology, Immunology, and Microbiology at Boston University and a researcher with MassCPR.

Snyder-Cappione was particularly intrigued by long COVID's overlap with the symptoms reported in a condition called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is

marked by profound fatigue, exhaustion, neurologic problems, sleep disturbances, headache, joint pain, shortness of breath, and palpitations. Like long COVID, ME/CFS tends to develop following certain viral and bacterial infections.

Studying those syndromes in parallel may bring insights about shared or similar mechanisms underlying these disorders. Even though many talented scientists have dedicated efforts to understanding postinfectious syndromes over the years, these efforts have been sporadic, Levy said, mainly because conditions like EBV, CMV, or Lyme disease, for example, have lacked the numbers and urgency of long COVID. This has led to less sustained funding to define their basic biology.

"Because of this new momentum, I am hopeful that research with long COVID patients presenting with these symptoms will result in novel treatments to help those afflicted with chronic conditions caused by other pathogens and insults," Snyder-Cappione said.

This is why MassCPR is expanding the mandate of its long COVID research group, co-led by Snyder-Cappione and Levy, to incorporate the study of other postinfectious disease syndromes. To reflect the new direction, the group will be renamed Post-Infectious Clinical Syndromes.

"We will start with that common ground," Levy said. "But then, as we excavate underneath the clinical surface, it'll be very interesting to see how shared or how discrete some of the molecular mechanisms are."

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