Pain researchers may know why COVID-19 spreads quickly in patients' lungs

June 25 2020, by Stephen Fontenot

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Around the world, scientists are racing to find ways to combat the symptoms of COVID-19 as the number of global cases surpasses 9 million. Researchers at The University of Texas at Dallas recently pinpointed a potential strategy for counteracting the acceleration of the illness in the lungs.

Fourteen scientists from the Center for Advanced Pain Studies (CAPS), a component of UT Dallas' School of Behavioral and Brain Sciences (BBS), collaborated on a project to determine if the pulmonary issues associated with SARS-CoV-2, the coronavirus that causes COVID-19, could originate with the nervous system.

Their study, published online June 1 in *Brain, Behavior, and Immunity*, identifies interactions between the immune system and nerves in the lungs that can cause rapid deterioration in a COVID-19 patient's condition. Some of these interactions might be countered by existing drugs, they said.

It's widely understood that severe cases of COVID-19 can have a major inflammation component that seems to start in the lungs, then affect the rest of the body. Analyzing publicly available data from patients in China, the CAPS team investigated this process as a potential case of neurogenic inflammation, in which the immune system and nervous system interact in a vicious cycle, leading to runaway inflammation.

"Most people, even biomedical researchers, don't fully appreciate how much the nervous system interacts with every organ in your body," said Dr. Ted Price BS'97, CAPS director and corresponding author of the study. "When you have a disease, the way the immune system and the nervous system interact is very important for the outcome of the disease. The better we understand this, the better we'll be at making sure that patients don't go from being pretty sick to being in the ICU and on a ventilator."

Cytokine storm

Price, the Eugene McDermott Professor of neuroscience, explained that COVID-19 patients who become severely ill mainly suffer from acute respiratory distress syndrome, or ARDS.

"These people can't get enough air from breathing to saturate their blood with oxygen, and that makes them very sick," Price said. "Some need ventilators; some people die from it."

In March, when Price initiated this research, knowledge of the course of the disease was still limited—but it had been noted that patients with ARDS had undergone what's known as a "cytokine storm," in which the body quickly releases too many of a broad category of signaling proteins produced by the immune system.

Dr. Michael Burton, a BBS assistant professor and co-author of the study, said the diversity of these interactions has only recently been understood.

"The prevailing school of thought in neuroimmunology used to be that immune cells signal sensory neurons to influence behavior," said Burton, whose research focuses on how the immune system and nervous system interact. "Recent studies have shown that the reverse also happens: Sensory neurons communicate with immune cells to control immune response. Pathogens can also interact directly with sensory neurons to help their own agenda—like how tuberculosis binds to sensory neurons to induce coughing for its spread and survival."

Burton said that this could be crucial context for the immune response in COVID-19 that is causing ARDS.

"A lot of treatments try to curtail the cytokine storm by targeting the immune cells themselves," he said. "But evidence from our study shows an interaction with neurons, immune cells and other cells in the lung that could provide a novel therapeutic targeting strategy."

Key protein

BBS research scientist Dr. Pradipta Ray, lead author of the paper, directed work on the creation of a computational method to examine how these nerve cells and immune cells react.

"We've done molecular profiling on the dorsal root ganglia—the peripheral nerve cells that innervate the lungs—and on immune cells from the lungs of severe COVID-19 patients in China, which were publicly available because scientists had published a paper," Price said. "From that, we merged these two profiles to look at how immune cells and nerve cells might interact, creating what we call an interactome. The results were very interesting."

In addition to the expected abundance of cytokines released by the immune cells that interacted directly with neurons, the presence of one particular protein stood out to the UT Dallas team.

"There's a striking increase in NMDA (N-methyl-D-aspartate) receptors in immune cells in the lungs that is much different than you see in other diseases," Price said. "It suggests that maybe the neurons there can communicate with the immune cells via glutamate, the neurotransmitter that NMDA receptors respond to. Interrupting this interaction might lessen the damaging effect."

The involvement of NMDA receptors is important because drugs already exist to block them.

The researchers said opportunities exist for clinical trials with in-development or existing rheumatoid arthritis drugs to treat high-risk or severe COVID-19 cases.

"There are already antagonists for NMDA receptors, so we have some targets to potentially block this neurogenic inflammation," Price said. "Such drugs might need to be used in combination for treatment,

however, because it's not just one simple molecule that's at the root cause—it's a whole host of them."

While the researchers established that a neuroimmune response is one way that COVID-19's most severe cases might spiral out of control, Price urged caution and said more research is needed to determine whether their insights might help patients.

"Our research indicates that in theory a neuroimmune process could play a huge role, and we show how that might play out. But we really still don't know to what extent neurogenic inflammation might actually cause this disease," Price said. "The science around COVID-19 is happening so fast; we're learning about the disease very quickly. I'm fairly confident we'll learn soon if our work is going to have an impact."

More information: Pradipta R. Ray et al. A pharmacological interactome between COVID-19 patient samples and human sensory neurons reveals potential drivers of neurogenic pulmonary dysfunction, *Brain, Behavior, and Immunity* (2020). DOI: 10.1016/j.bbi.2020.05.078

Provided by University of Texas at Dallas