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Plasmin could be the link between COVID-19 comorbidities and serious illness

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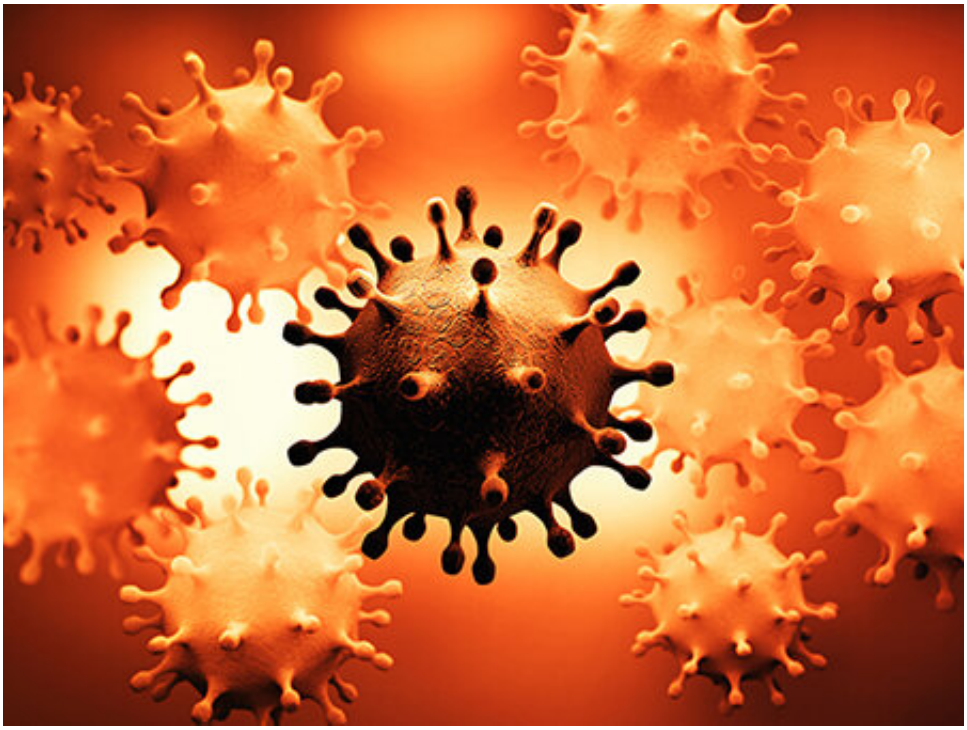

A drug that inhibits the protease plasmin is hypothesized to reduce the infectivity and virulence of the virus, as measured by reduced need for hospitalization within a week. Credit: UAB

Why is the COVID-19 virus more dangerous in people with comorbidities?

Sadis Matalon, Ph.D., of the University of Alabama at Birmingham and

colleagues in Texas and San Francisco asked that question in a hypothesis paper published online in *Physiological Reviews*. This study was made available online in March 2020 ahead of final publication in issue on July 1, 2020. They reviewed, in detail, research literature for comorbidities like hypertension, diabetes, coronary heart disease, cerebrovascular illness, chronic obstructive pulmonary disease and kidney dysfunction, as well as many viral studies, studies of COVID-19 pathology and clinical presentation, and literature on the life-threatening acute respiratory distress syndrome.

Twelve days later, UAB Professor Emeritus Timothy Ness, M.D., Ph.D., posted plans on ClinicalTrials.gov for an exploratory COVID-19 outpatient study to test Matalon's hypothesis and prevent worse clinical outcomes.

In the *Physiological Reviews* paper, the researchers noted that all those comorbidities feature elevated levels of the extracellular protease plasmin. Plasmin is able to nick proteins at amino acid sequences called furin sites. For many viruses, this nicking at furin sites increases their infectivity. Both SARS and MERS—the two virulent coronaviruses that are related to the COVID-19 virus—"have evolved an unusual two-step furin activation for fusion, suggestive of a role during the process of emergence into the human population," the researchers wrote.

They noted that the COVID-19 virus, SARS-CoV-2, also has a furin site on its spike protein, the vital, viral protein for viral attachment to a lung cell. The researchers proposed that plasmin may cleave that furin site in the spike protein to increase its infectivity and virulence, and they hypothesized that, "the plasmin system may prove a promising therapeutic target for combating COVID-19."

Ness already knew there is an inexpensive, commonly used drug—tranexamic acid, or TXA—that targets plasmin by inhibiting its

conversion from the inactive precursor, plasminogen, to the active protease, plasmin.

TXA is approved by the U.S. Food and Drug Administration for treatment of heavy menstrual bleeding because having lower plasmin levels allows better clotting. TXA has a long track record of safety and is commonly given off-label. At UAB Hospital, TXA is used perioperatively as a standard-of-care for orthopedic and cardiac bypass surgeries; it is commonly used for hemorrhaging trauma patients and also has been used for spinal surgery, neurosurgery and corrective jaw surgeries. It is currently being studied for perioperative use in Cesarean section surgeries.

For the clinical trial, Ness and colleagues have started a double-blind study, giving either TXA or a placebo pill to COVID-19 outpatients who were recently diagnosed with COVID-19. Patients also receive an anticoagulant. The overall goal of the exploratory study is to assess both safety and efficacy of five days of TXA versus placebo in the COVID-19 population. Enrollment is ongoing.

Ness and colleagues hypothesize that the TXA treatment will reduce the infectivity and virulence of the virus, as measured by reduced need for hospitalization within a week if a patient's condition deteriorates. Adults 19 years old and older are eligible, and all patients—whether in the control group or the TXA group—receive standard care as directed by their primary caretakers.

Matalon says the paper has been widely noticed. "Since its publication online, it has been downloaded 26,565 times and cited 55 times," he said.

More information: Hong-Long Ji et al, Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility, *Physiological*

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