Sugar-binding protein galectin-1 could be a biomarker for patients at risk of life threatening sepsis

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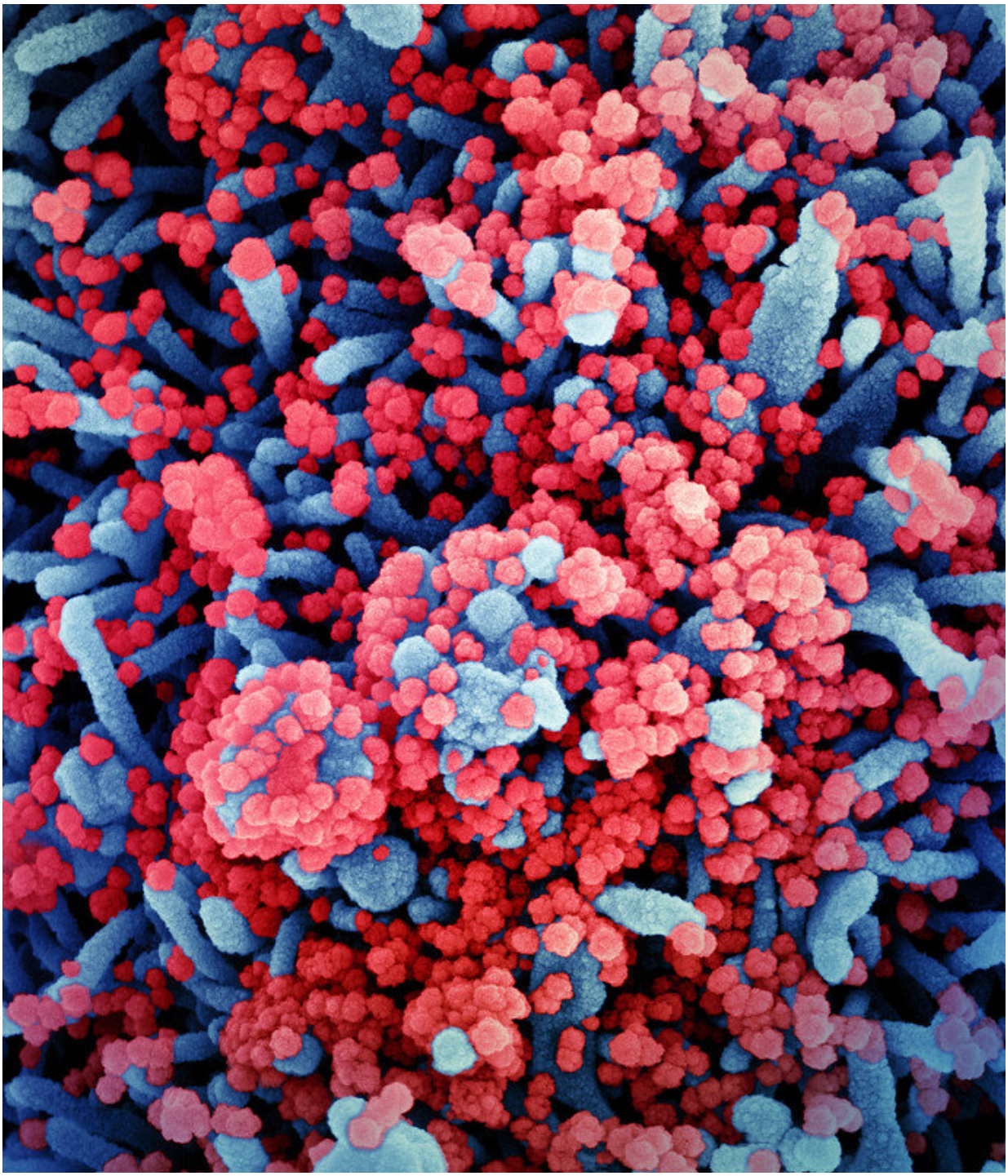

Colorized scanning electron micrograph of a cell (blue) heavily infected with SARS-CoV-2 virus particles (red), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

A sugar-binding protein could fuel terrible inflammation and worsen sepsis, a disease that kills more than 270,000 people every year in the US alone, reports a team of researchers led by UConn Health in the 4 January issue of *Nature Immunology*.

Sepsis is caused mostly by bacterial infections. The immune system runs out of controls and triggers a cytokine storm, a condition in which inflammation-causing proteins flood the blood. Organs may break down, and death often follows.

Other diseases can also cause cytokine storms; medical historians believe cytokine storms were behind the lethality of the 1918-1919 flu epidemic, as well as the Black Death. Cytokine storms are also observed in patients with severe COVID-19 and believed to be involved in death in COVID-19.

A main trigger for the cytokine storms during sepsis is the overreaction of the body when it detects an infection inside the cells. When a cell detects bacteria or pieces of bacteria inside itself, it immediately activates enzymes that in turn activate a protein that pokes holes on the cell membrane from within, eventually causing the cell to burst open and spill cytokines into the bloodstream. Cytokines are alarm signals, calling in the immune system to fight the bacteria. Cytokines also make other cells more likely to burst open and sound the alarm. Usually, the system damps itself after a while and calms down, but in sepsis it spins out of control, causing more and more cells to burst and die and release even more cytokines into the bloodstream.

When cells burst open, they release not only cytokines, but also other danger molecules called alarmins that alarm the body of an infection or injury and can amplify the ongoing cytokine storm.

UConn Health immunologist Vijay Rathinam wanted to know which alarmins were released when a cell detected a specific kind of bacterial molecule called lipopolysaccharide inside itself. Dr. Ashley Russo, then a graduate student in the Rathinam lab, catalogued—in collaboration with immunologists Tony Vella and Antoine Menoret at UConn Health—proteins released by these cells when they detected lipopolysaccharide.

And they found something exciting. Galectin-1, a protein that binds sugars and sugar-coated proteins, seemed to be emanating from the cells. Interestingly, they found that galectin-1 is small enough to be slipping out of the holes poked in the cells' membrane, even before the cells burst open.

Once they noticed that, they began to look at the role galectin-1 played in sepsis. They found that galectin-1 seemed to be suppressing a brake on inflammation, causing the cytokine storm to ramp up. They also found that mice lacking galectin-1 had less inflammation, less organ damage, and survived longer than normal mice did during sepsis resulting from a bacterial infection and lipopolysaccharide.

To find out if galectin-1 is released during sepsis in human patients, the team collaborated with the Jena University Hospital's Drs. Deshmukh, Bauer, and Sponholz and found that sepsis patients had higher levels of galectin-1 than other non-sepsis patients in critical care and healthy people.

The team is considering whether galectin-1 might be a good drug target to help dampen cytokine storms during sepsis, as well as a useful marker doctors could use to identify critical ill patients at risk.

More information: Ashley J. Russo et al, Intracellular immune sensing promotes inflammation via gasdermin D–driven release of a lectin

alarmin, *Nature Immunology* (2021). DOI: 10.1038/s41590-020-00844-7