Identifying therapeutic targets in sepsis' cellular videogame

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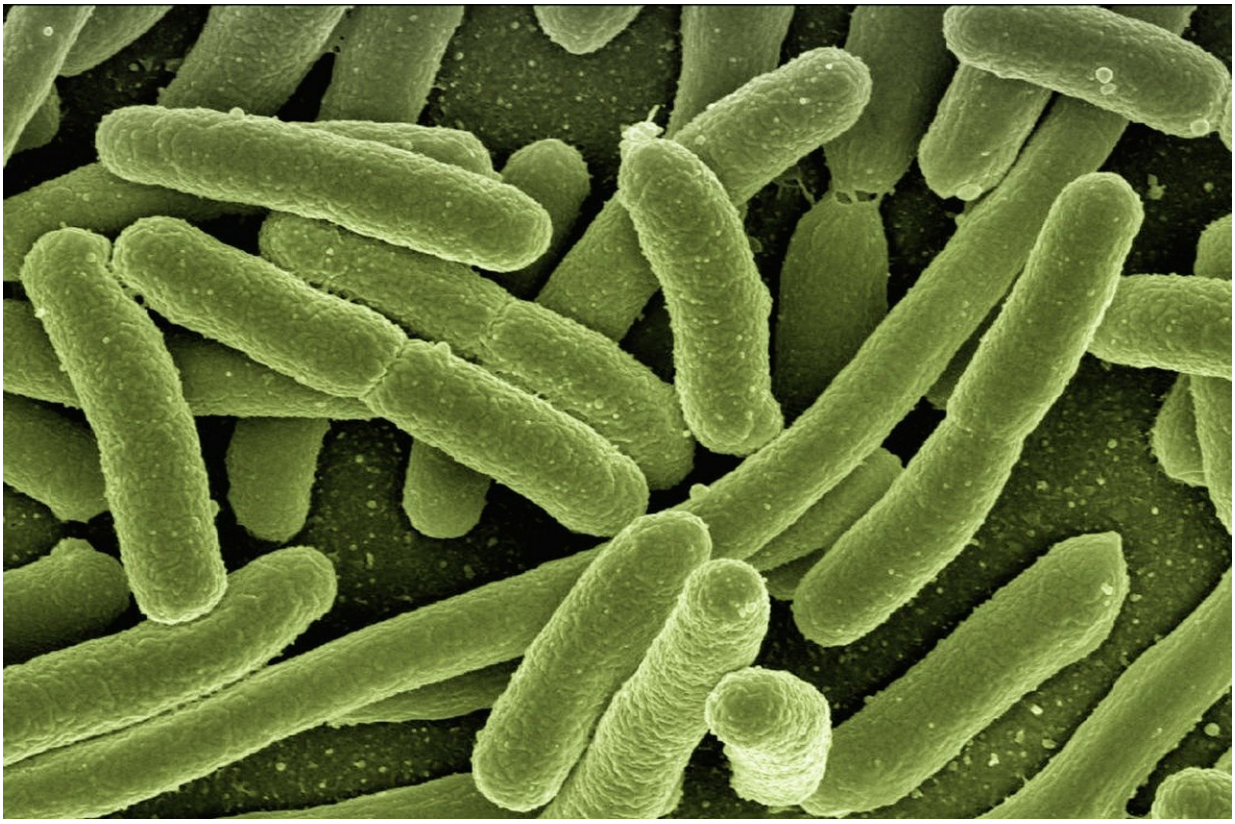

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Sepsis is a medical condition that few patients have heard of and most doctors dread. The body's response to attack by bacteria can trigger a cascade of cellular self-destruction that inadvertently causes blood clots,

multi-organ failure, and death.

The immune system functions as a sort of cellular Pac-Man, using white blood cells to hunt out the "bad guys," initiating attacks and counter-attacks. However, in extreme cases, white blood cells commit a sort of hara-kiri, triggering their own death in an attempt to destroy the infection. Sometimes it works—but when it doesn't, the complications are dangerous.

The arsenal of weapons to treat severe cases of sepsis is miserably small, and physicians have little to provide other than antibiotics, fluids, and hope. Exciting new research has defined the chain of molecular events that goes awry in sepsis, opening up opportunities for new treatments to fight the condition that affects more than a million Americans each year and kills up to a third of them.

Two collaborating laboratories at the University of Kentucky were able to establish the events within white blood cells that progresses from inflammasome activation to a type of programmed cell death called pyroptosis—and culminates in the damaging blood clots.

"Recent studies have uncovered the mechanism of pyroptosis following inflammasome activation, but we didn't know how pyroptotic cell death drives the disease process," said Zhenyu Li, M.D., Ph.D., an associate professor in the University of Kentucky's Department of Molecular and Cellular Biochemistry.

"If we could uncover that link, it would open up possibilities for therapies that target inflammatory, infection-mediated clotting."

The teams, led by Li and Yinan Wei, Ph.D. of UK's Department of Chemistry, determined that certain bacterial proteins and endotoxin trigger inflammasome activation in white blood cells, causing pyroptosis.

During pyroptosis, pores form in the white blood cell membrane that result in the release of tissue factor, a protein known to initiate the clotting process.

"Our data establish inflammasome activation as an important link between inflammation and blood clotting," Li said. "Our findings advance the understanding of the relationship between bacterial infections and coagulation as well as provide evidence that inflammasome may be a potential therapeutic target for sepsis."

The data was published online this week in advance of its June publication in Cell Press' *Immunity*.

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