Discovery could help treat fatal, drug-resistant pneumonia and sepsis

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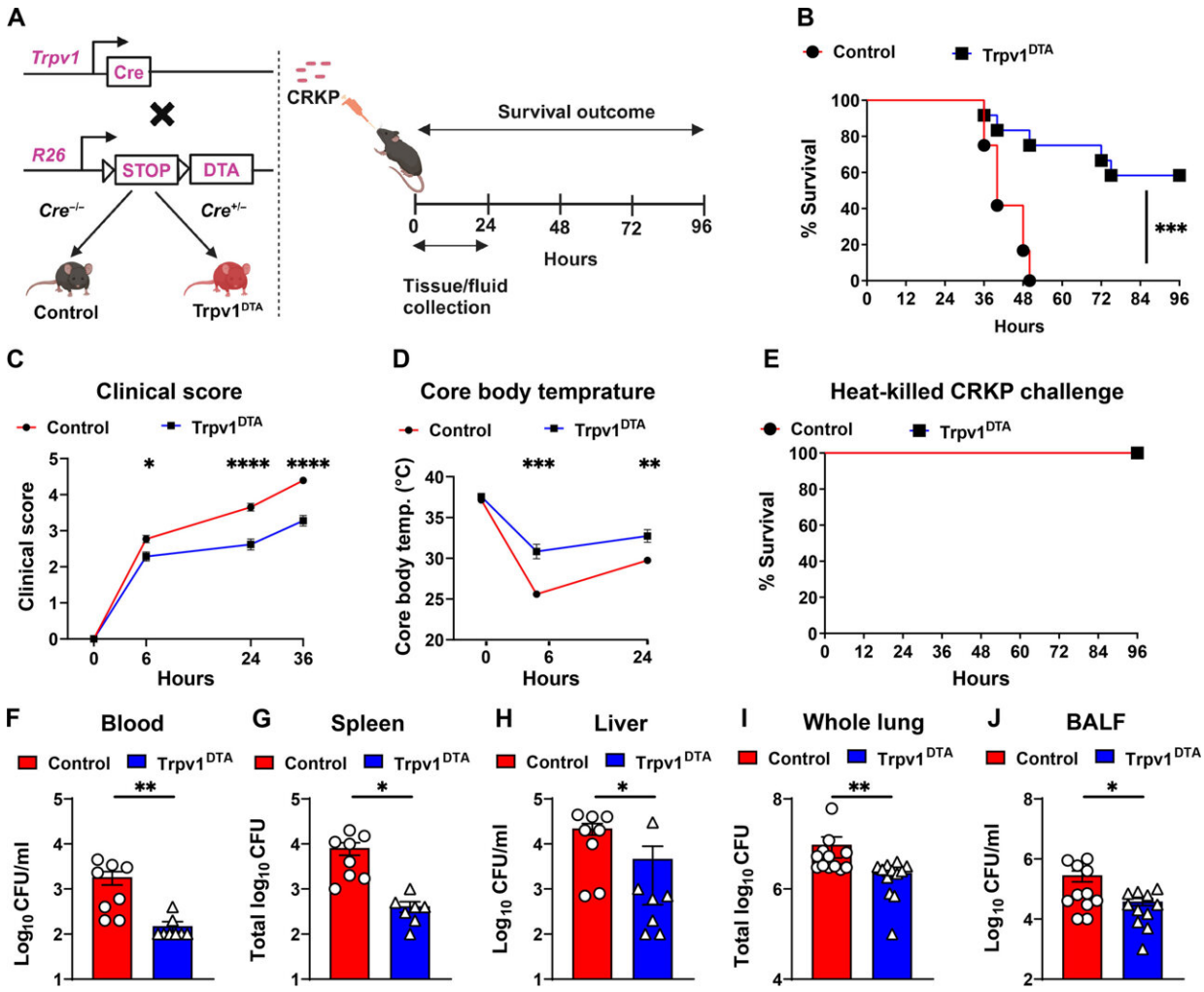

Nociceptor neurons suppress host protection against CRKP pneumonia and pneumonic sepsis. Credit: *Science Advances* (2024). DOI: 10.1126/sciadv.adl6162

Bacterial pneumonia and sepsis are leading causes of hospitalization and death. Researchers in Kansas State University's Division of Biology have discovered that dysfunction of the body's immune response to bacterial infection may be part of the problem.

Pankaj Baral, assistant professor of biology, and Prabhu Raj Joshi, doctoral student in microbiology, are studying how nervous and immune system crosstalk, or bilateral signaling, impacts the body's ability to fight pneumonia caused by the Gram-negative bacteria known as carbapenem-resistant Klebsiella pneumoniae, or CRKP.

The researchers published their study, "Lung-innervating nociceptor sensory neurons promote pneumonic sepsis during carbapenem-resistant Klebsiella pneumoniae lung infection," in *Science Advances*.

CRKP bacteria are the most common cause of hospital-acquired lung infections and are a major contributor to fatal pneumonia-induced sepsis, or pneumonic sepsis, among hospitalized patients. The U.S. Centers for Disease Control and Prevention considers CRKP and other Gram-negative bacteria an urgent public health threat and states that an alternative non-antibiotic treatment for Gram-negative pneumonia and pneumonic sepsis is essential.

Baral and Joshi's study investigated the role of neuroimmune signaling in bacterial pneumonia, focusing on lung-innervating nociceptor sensory neurons—neurons that mediate pain—during lung infection with CRKP.

Normally, the sensory nervous system protects the body by sensing and responding to noxious stimuli. However, the study showed that during lung infection by CRKP, the sensory nervous system is detrimental, and lung-innervating sensory neurons, meant to defend against pneumonia and sepsis, seem to be the culprit.

"Our study showed that nociceptor activation and pain sensations, normally considered critical defense mechanisms, actually enhance CRKP infection and pneumonia lethality," said Joshi. "So, we think that CRKP might employ nociceptor neuron activation to establish infection and cause severe disease such as sepsis."

This discovery could help scientists develop a non-antibiotic sepsis treatment that targets nociceptor neurons or blocks their receptor signaling pathways.

In fact, the team is collaborating with researchers at the University of Kansas to perform high-throughput screening of small molecules to identify the most potent chemical inhibitors of nociceptor signaling for use as a therapeutic treatment for Gram-negative pneumonia and sepsis.

More information: Prabhu Raj Joshi et al, Lung-innervating nociceptor sensory neurons promote pneumonic sepsis during carbapenem-resistant Klebsiella pneumoniae lung infection, *Science Advances* (2024). DOI: 10.1126/sciadv.adl6162

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