Scientists stumble upon a model to study a lethal complication

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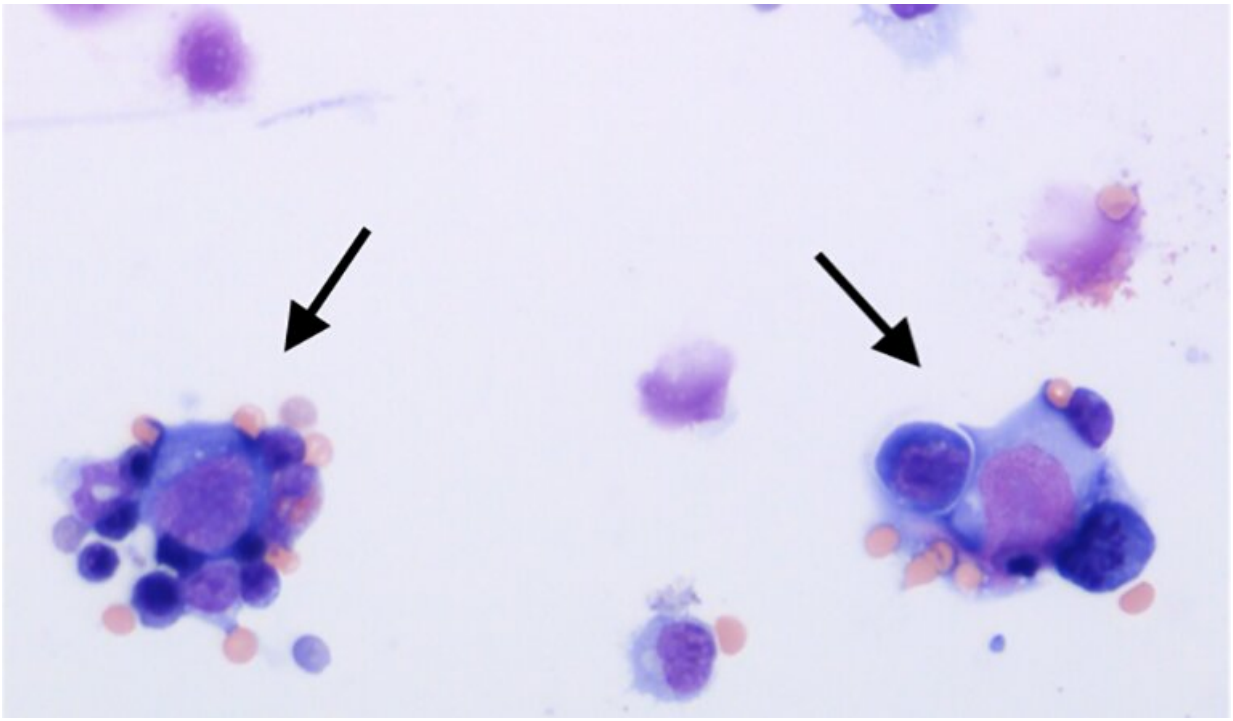

Image shows signs of a lethal complication, hemophagocytosis, in the bone marrow after sequential inflammatory challenge. Credit: Yale University

More and more hospitalized patients with sepsis are being diagnosed with a deadly complication characterized by high levels of inflammation. A team of Yale researchers has uncovered clues to the cause of this complication—which kills up to 80% of patients—and a potential new

strategy for treating it.

The research team, led by Andrew Wang in the lab of Ruslan Medzhitov, was studying metabolism in mice exposed to different bacterial and viral infections. They stumbled upon a particularly fatal mix of infections, which resembled a complication in humans known as either sHLH or macrophage activation syndrome. This discovery allowed them to study the condition in an animal model for the first time.

With this model, the research team learned that in animals with sHLH, specialized cells known as macrophages are over-stimulated and start devouring immune cells and red blood cells. By sequencing the macrophage genes, they were able to identify a marker of the condition—a transcription factor called SpiC. Through further experiments, the researchers found that the macrophages were dependent upon glucose metabolism to thrive, and that with a drug designed to block glucose, they could reduce inflammation and save the mice.

The study findings provide the researchers with a signature to test patients who might have sHLH. The results could also lead to better treatment. "There seems to be a close relationship between inflammation biology and metabolism," said Wang. "Most drugs are designed to block mediators in inflammation. In this study, we have proof of concept that you could target inflammation by targeting metabolism."

More information: Andrew Wang et al. Specific sequences of infectious challenge lead to secondary hemophagocytic lymphohistiocytosis-like disease in mice, *Proceedings of the National Academy of Sciences* (2019). DOI: 10.1073/pnas.1820704116

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