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Single Enzyme Helps Drive Inflammation in Mice, Provides Target for New Sepsis Drugs

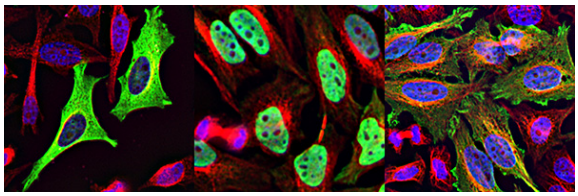
Sepsis occurs when the body goes overboard in its attempt to fight off an infection. Immune cells rush in, overreact and wreak havoc on tissues and organs, often resulting in organ failure and death.

Researchers at University of California San Diego School of Medicine recently found that removing the enzyme PHLPP1 improved outcomes in a mouse model of sepsis. PHLPP1 controls many cell behaviors by removing phosphates (small chemical tags) from other proteins. And, it now turns out, PHLPP1 also influences inflammation.

The study, published August 13, 2019 in *eLife*, introduces the possibility that inhibiting PHLPP1 could form the basis for new sepsis treatments in humans.

“Most research on inflammation has typically focused on kinases, enzymes that add phosphate tags to other proteins,” said senior author Alexandra Newton, PhD, professor in the Department of Pharmacology at UC San Diego School of Medicine. “It’s exciting to have a completely new target for sepsis — the enzymes that remove them.”

Newton’s team discovered PHLPP1 a few years ago and have since detailed its role in suppressing tumors. Following up on these findings, Newton reached out to UC San Diego School of Medicine colleague Chris Glass, PhD, an expert on inflammation.



HeLa cells expressing PHLPP (left), the segment with the nuclear localization signal (middle), and that same segment mutated (right).

Together, their teams uncovered many immune cell genes that are influenced by PHLPP1. But PHLPP1’s particular influence on inflammation could be linked to the fact that it removes phosphates from a transcription factor called STAT1, which is known for controlling inflammatory genes.

Newton's team took mice modified to lack the PHLPP1 gene to another UC San Diego School of Medicine colleague, Victor Nizet, MD, an expert on bacterial infections. In separate experiments, Nizet's team administered live *E. coli* bacteria and lipopolysaccharide (LPS), a component of the bacterium's cell wall that drives immune systems wild, to both PHLPP1-deficient and normal mice.

The difference surprised Newton: Mice without PHLPP1 fared much better. While all normal mice died of the infection-induced sepsis after five days, half of the PHLPP1-deficient mice survived.

Newton's team had already been working with additional collaborators to screen thousands of chemical compounds to identify those few that inhibit PHLPP1. Now that they know PHLPP1 inhibitors might form the basis for new anti-sepsis drugs, the researchers hope to test these compounds on immune cells in the lab and in the mouse model of sepsis.

Currently, sepsis is addressed by preventing and treating the source infection, often with antibiotics, while maintaining organ health with oxygen and intravenous fluids. Nonetheless, according to the Centers for Disease Control and Prevention, at least 1.7 million adults in the U.S. develop sepsis each year, and nearly 270,000 die as a result. One in three patients who die in a hospital have sepsis.

"Sepsis is the leading cause of death in intensive care units throughout the world, but unfortunately there is not a single approved drug treatment for sepsis," Nizet said. "Discoveries like ours of fundamental signaling pathways that control immune cell behavior during sepsis offer clues for controlling the dangerous inflammation of sepsis while preserving the critical bacterial killing properties of white blood cells."

Co-authors include: Ksenya Cohen-Katsenelson, Joshua D. Stender, Agnieszka T. Kawashima, Gema Lordén, Satoshi Uchiyama, all at UC San Diego.

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Disclosure: Victor Nizet is a co-founder and scientific advisor for Staurus Pharma, LLC and has equity interest.

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