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Wistar Scientists Discover How Gut-Derived Metabolite Acts as Immune "Volume Knob" Via Macrophages

PHILADELPHIA — (JAN. 29, 2026) — Scientists at The Wistar Institute have identified a previously overlooked mediator in the body's response to life-threatening infections: hippuric acid, a metabolite produced when gut bacteria break down polyphenols from berries, tea, and other plant-based foods. The research reveals that this molecule acts as an immune-system amplifier, boosting the body's inflammatory defenses during early infection but elevating them to deadly levels when infections progress to sepsis.

Published in *Cell Reports*, the study demonstrates that elevated hippuric acid levels correlate with increased mortality in sepsis patients, while also uncovering the molecular mechanisms by which this metabolite modifies immune responses. The findings could lead to new approaches for managing severe infections and, potentially, for treating pancreatic cancer.

"Hippuric acid is a metabolite that has historically been seen as a benign byproduct of metabolism and is therefore understudied," said **Rahul S. Shinde, D.V.M., Ph.D.,** assistant professor in the Molecular and Cellular Oncogenesis Program at the Ellen and Ronald Caplan Cancer Center at The Wistar Institute and senior author of the study. "This paper identifies that it's not just a passive byproduct. It has bioactive potential to influence the immune system."

Shinde's team discovered the bioactive potential of hippuric acid while performing a metabolomic screening on preclinical models infected with *E. coli.* They found that hippuric acid levels fell 24-fold within 48 hours of infection, suggesting the molecule played an active role in the immune response.

To understand what hippuric acid was doing, the researchers administered it to infected preclinical models. They found that the metabolite acted like a volume dial for inflammation, amplifying the production of pro-inflammatory molecules like IL-12 and IL-6 while suppressing anti-inflammatory signals. Together, these results suggest that a compound once thought to be a passive metabolic byproduct can actively push the immune system toward a dangerous overreaction. When the researchers examined human sepsis patients, they found that those with elevated hippuric acid levels were significantly more likely to die.

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Through a series of experiments using cultured immune cells, genetically modified preclinical models, and advanced molecular profiling techniques, Shinde's team uncovered how hippuric acid amplifies inflammation. The metabolite works by enhancing an immune signaling pathway involving Toll-like receptor (TLR) and MyD88 proteins, which act as the immune system's early warning system for detecting pathogens. Hippuric acid makes these immune system detectors more sensitive and boosts the phosphorylation of key signaling proteins like IRAK4 and NF-κB, amplifying the inflammatory cascade once it's begun. (Notably, the effects of hippuric acid require activation of the MyD88 signaling protein. In preclinical models lacking MyD88, hippuric acid had no impact on inflammatory responses.)

The researchers also discovered that by triggering TLR signaling, hippuric acid causes macrophages to produce more cholesterol and remodel their lipid composition—changes that further sustain their inflammatory state. When the team blocked cholesterol synthesis using drugs like fluvastatin, the pro-inflammatory effects of hippuric acid disappeared, demonstrating that lipid metabolism is integral to the metabolite's immune-boosting function.

"It's a chain of events," said Shinde. "Hippuric acid is acting via the TLR/MyD88 pathway and promoting the inflammatory signal, inflammatory responses go up, and then genes that are part of lipid remodeling in macrophages get activated, contributing to inflammation."

While significant for sepsis patients, whose survival may improve from monitoring or modulating hippuric acid levels, these findings could have even broader potential for cancer treatment. Shinde's lab focuses on pancreatic cancer, one of the deadliest malignancies with a five-year survival rate of just 13%. In solid tumors like pancreatic cancer, macrophages often become immunosuppressive, creating a protective shield around cancer cells that prevents T cells from attacking them. Shinde and his team are investigating whether these macrophages can be reprogrammed to be immunostimulatory instead of immunosuppressive.

"We want to get them to become immunostimulatory so that instead of making a shield, they kick T cells into action to attack cancer cells," Shinde said. "My lab is particularly interested in whether we can harness microbial metabolites like hippuric acid to do that job. We'd love to take a natural approach where we balance the diet and microbiome in patients with cancer to change macrophage behavior."

The team is conducting preliminary studies in preclinical models of pancreatic cancer and investigating how hippuric acid affects TLR signaling and cholesterol metabolism in tumor-associated macrophages. They are also working to understand the long-term effects of hippuric acid exposure through diet on baseline immune function.

"We want to understand the impact of hippuric acid levels on a chronic basis. If somebody eats blueberries and a polyphenol-rich diet, is it helpful over the long term or not?" said Shinde. "These things really shape health outcomes."

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