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Scientists uncover the way a common cell enzyme alerts the body to invading bacteria

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Biomedical investigators at Cedars-Sinai have identified an enzyme found in all human cells that alerts the body to invading bacteria and jump-starts the immune system.

In their study, published in the peer-reviewed medical journal *Cell*, the investigators provide clues to unraveling some of the mysteries surrounding the human immune system, which defends the body against harmful microbes such as bacteria.

The finding helps explain how the immune system "knows" certain bacteria are harmful. It also may shed light on why common health conditions such as obesity, Type 2 diabetes and coronary artery disease often are accompanied by inflammation.

"Decoding how the immune system works is one of the most urgent lines of inquiry in medical research today," said Shlomo Melmed, MD, dean of the Cedars-Sinai medical faculty, executive vice president of Academic Affairs and the Helene A. and Philip E. Hixon Distinguished Chair in Investigative Medicine. "This study makes a major contribution to the field of immunology and helps us better understand disease processes as we search for new treatments to help our patients."

Generally, scientists divide the human immune system into two parts. One part, called the innate immune system, allows for immediate and direct recognition of invading bacteria. It prompts immune cells to kill, eat and degrade the microbes and also triggers inflammation to fend off

their attack. This activity alerts the body's second line of defense, the adaptive immune system, which includes production of antibodies.

The new Cedars-Sinai study identifies a metabolic enzyme doing "double-duty" as a gatekeeper for the innate immune system. The investigators found that hexokinase, a common enzyme necessary for cells to use glucose as a source of energy, binds to a sugar in peptidoglycan, a chemical compound in cell walls of many harmful bacteria. This binding action triggers the activation of protein complexes that direct strong inflammatory responses against bacteria.

Although the research was performed largely in cells from laboratory mice, the investigators later found similar mechanisms operating in human cells.

"Hexokinase is not a protein specific to the immune system," said David Underhill, PhD, professor of Biomedical Sciences, research scientist in the F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute at Cedars-Sinai and the study's principal investigator. "All cells have hexokinase. It's required to make energy. The dual role of this enzyme in metabolism and innate immunity is surprising."

The discovery of hexokinase's two functions has far-reaching implications. It may help explain why chronic, low-level inflammation often is found in patients with obesity, Type 2 diabetes and coronary artery disease. These serious conditions, which affect millions of Americans, are intertwined with metabolism—the chemical processes by which the body uses food and other substances to make energy, grow and heal.

To explore a possible link between metabolism and inflammation, the investigators used chemical means to disrupt metabolism and interfere with hexokinase's function in mouse cells in a petri dish. They found that

this disruption was enough to activate the bacteria-fighting protein complexes. While the exact mechanism was not clear, the data suggest an intriguing relationship between cellular metabolism and inflammatory signaling.

"The observation that altering a metabolic process causes inflammation may have profound implications for diseases, including diabetes, obesity, atherosclerosis and inflammatory bowel disease," said Andrea Wolf, PhD, a project scientist in Underhill's laboratory and the study's first author. "Now, we are continuing our research so we can learn exactly how the enzyme activates inflammation."

Provided by Cedars-Sinai Medical Center