Confronted with sepsis, key immune mechanism breaks, scientists find

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When the body encounters an infection, a molecular signaling system ramps up the body's infection-fighting system to produce more white blood cells to attack invading bacteria. Now researchers have discovered that when facing a massive bacterial infection resulting in sepsis, that same signaling system malfunctions, damaging the body's ability to fight the invaders.

In addition to suppressing the mature blood cells battling against the infection, malfunctioning of this signaling system results in permanent damage to the body's blood producing cells - called hematopoietic stem cells - that are located in the bone marrow. The research, by scientists at the Indiana University School of Medicine, was published recently in the journal *Stem Cell Reports*.

Sepsis is a life-threatening response by the body's inflammatory system that can result from severe bacterial infections. It is a growing problem: The number of hospitalizations for sepsis more than doubled from 2000 to 2008, reaching more than 1.1 million, according to the Centers for Disease Control and Prevention. Patients with severe sepsis or septic shock have a mortality (death) rate of about 40%-60%, with the elderly having the highest death rates. Newborns and pediatric patients with sepsis have about a 9%-36% mortality rate.

"Our goal is to find out what causes this bone marrow failure during serious infections, and find ways to prevent it," said Nadia Carlesso, M.D., Ph.D., professor of pediatrics and of medical and molecular

genetics at the IU School of Medicine.

Most research has focused on understanding and managing the late consequences of sepsis while little is known about the changes occurring in the bone marrow at early stages of the response to bacterial infection, when the opportunity for effective treatment might still be available. Dr. Carlesso's group has pioneered the study of bone marrow responses during acute infection. Using laboratory models of severe sepsis her group has discovered that the blood-producing stem cells fail to continuously generate mature neutrophils, which are the most critical bacteria-fighting cells.

"In this research we determined that in cases of severe infection and sepsis, a key mechanism in the body's response to infection is broken. These findings point to potential new targets for protecting the immune system during major infections," Dr. Carlesso said.

The IU researchers focused on a set of proteins called toll-like receptors, which function as sentinels on the surfaces of cells. When the receptors detect the presence of invading bacteria, they send signals to the body's immune response system. The IU researchers looked at toll receptor 4 (TLR4), which activates two signaling pathways that stimulate the production of more neutrophils during common infections, but suppress it during severe infections.

In a laboratory model of sepsis using mice, the researchers found that two abnormal effects activated by toll receptor 4 during severe infection—the suppression of neutrophil production and the damage to the bone marrow's blood-producing stem cells—are mediated by two different molecules downstream of TLR4.

"This study is a good start, as provides a more precise map to follow, but more research is needed to better understand this process and develop

better, and much needed, therapeutic strategies for sepsis," said Dr. Carlesso.

More information: Huajia Zhang et al. Sepsis Induces Hematopoietic Stem Cell Exhaustion and Myelosuppression through Distinct Contributions of TRIF and MYD88, *Stem Cell Reports* (2016). DOI: 10.1016/j.stemcr.2016.05.002

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