Smarter treatment for killer infections

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Sepsis is a major killer in hospital intensive care units. Researchers at Case Western Reserve University School of Medicine have found that manipulating a genetic factor that can launch or throttle the body's defenses can improve survival rates during bacterial infection.

"Currently, our therapies for sepsis are very limited," said Mukesh K. Jain, MD, Ellery Sedgwick Jr. Chair, director of the Case Cardiovascular Research Institute, and professor of medicine at Case Western Reserve University School of Medicine and chief research officer of the Harrington-McLaughlin Heart & Vascular Institute at University Hospitals Case Medical Center.

Lead author Ganapati H. Mahabaleshwar, PhD, assistant professor of medicine at Case Western Reserve School of Medicine spearheaded the effort, which included researchers from St. James Hospital, Dublin, Ireland; and the University of Cincinnati College of Medicine. They discovered that indiscriminately boosting immune cells may cause harm and even death. Surprisingly, when a patient is suffering from the end-stage of sepsis, the defense system needs to be curbed to prevent the body's own immune cells from contributing to shock and death.

The work is published in the 27 May 2011 edition of the journal *Immunity*.

The key to better sepsis therapies is knowing when to turn up or turn down the factor, called Kruppel-like transcription factor 2, or KLF2 for short, says Dr. Jain, the senior author of the study.

Inside immune cells called macrophages, KLF2 acts like a concert mix-master. But, instead of adjusting the base and feedback, the factor adjusts cell activities according to signals from the internal environment.

Normally, the factor maintains immune cells in a quiet state. But during the first phase of sepsis, when bacteria begin to attack, the resulting low oxygen levels and high amounts of bacterial products cause the level of KLF2 to be reduced.

The reduction in KLF2 essentially opens the gates for macrophages to release noxious products that kill bacteria, the investigators found.

But when sepsis moves into the second phase, marked by low body temperature and blood pressure, tissue damage, and a cascade of organ shutdowns, the body's own defenses are doing harm by promoting inflammation that can cause shock and death.

"In this phase, it's time to boost KLF2 and quell unbridled inflammation," says Dr. Jain.

The body, however, does not do this naturally. The researchers don't know why but suspect that continued hypoxia and leaching of bacterial products into circulation keep KLF2 levels low.

The research builds on the Jain lab's 2006 discovery of KLF2 in macrophages. In the new study, testing showed that mouse models deficient in KLF2 were effective in defeating polymicrobial infections in the early stage of infection. But, in testing the late-stage of sepsis, mouse models lacking KLF2 were more likely to die and die sooner.

Testing of blood samples taken from hospital patients suffering from sepsis produced the same patterns.

The team is now looking for compounds that could reduce the amount of KLF2 in the first phase of infection, and other compounds to bolster levels in the second phase.

Dr. Jain's group, as well as other researchers, have found that statins, the class of drugs used to reduce cholesterol levels, and resveratrol, the substance in red wine credited with boosting good cholesterol, may be useful in combating sepsis. Dr. Jain's team suggests that the timing of administration of such therapies may determine how patients respond to sepsis.

Provided by Case Western Reserve University