Immune responses to mitochondria help explain body's inflammatory response to injury

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Inflammation is at the root of most serious complications occurring after both infection and injury. But while the molecular course of events that leads from microbial infections to the inflammatory condition called sepsis is fairly well understood, it is far less clear how and why physical injury can result in a similarly dangerous inflammatory response.

Now a study led by investigators at Beth Israel Deaconess Medical Center (BIDMC) suggests that mitochondria - the body's cellular "power plants" -- are released into the bloodstream following physical injury. And because mitochondria closely resemble the bacteria from which they originated, they appear to elicit a sepsis-like immune response, changing from a vital source of cellular injury to a dangerous "enemy within."

Appearing in tomorrow's issue of the journal *Nature*, the findings could eventually lead to new strategies in the management of trauma as well as to the development of new tests to help clinicians discriminate between infective and non-infective inflammation.

"The body's vital organs can become dysfunctional when traumatic injury triggers the Systemic Inflammatory Response Syndrome, or SIRS," explains senior author Carl J. Hauser, MD, a trauma and critical care surgery specialist at BIDMC and Visiting Professor of Surgery at Harvard Medical School. "Trauma kills 5 to 10 million people worldwide

per year and among U.S. individuals under age 35, trauma accounts for more deaths than all other illnesses combined. Inflammatory complications are directly responsible for about one-third of those deaths."

Hauser, whose laboratory studies focus on neutrophils, circulating white blood cells that can attack the body's organs, wanted to find out how neutrophils might be participating in this dangerous inflammatory cascade.

The mechanisms that underlie both SIRS and sepsis are rooted in the body's "innate immune" response. Unlike "acquired immunity," which develops over time, innate immunity is present from birth, ready to immediately respond whenever immune cells encounter molecular patterns typical of external pathogens such as bacteria or viruses. These "pathogen-associated molecular patterns," or PAMPS, are in turn, detected by pattern recognition receptor molecules (PRR).

"When an infection strikes, PAMPs activate PRR very rapidly, initiating a group of cellular responses collectively described as the 'Danger Response,'" explains Hauser. This response underlies both SIRS and sepsis, and can ignite early reactions to cell threats as well as act as an adjuvant for later acquired immune responses. However, as Hauser notes, infectious pathogens and PAMPs aren't the only cause of the Danger Response.

"Injured or necrotic tissues can activate very similar immune responses," he explains. "Blunt-force trauma can result in the death of significant amounts of tissue, as can burns, cancer chemotherapy, major surgeries and many other diseases. We wondered if tissues that die by such pathologic means, rather than via programmed cell death or apoptosis, were releasing into the body molecular debris not normally encountered by the immune system."

Some normally intra-cellular molecules can activate PRR, and when they do they are called Damage-Associated Molecular Patterns, or DAMPS. Hauser hypothesized that DAMPs might be triggering inflammatory responses after trauma in the same way that PAMPs triggered inflammation in the face of infection -- and that mitochondria might be ultimately responsible.

Mitochondria are structures within cells that burn nutritional energy sources using oxygen and convert it into the ATP that powers the cells. They function autonomously, having their own DNA which is separate and very different from the genetic material contained within the cell's nucleus, and their own machinery for protein synthesis. Because mitochondria share so many similarities with bacteria - including their method of reproduction, the molecular nature of their DNA and their synthesis of n-formylated proteins - it is believed that they were once free living bacterial saprophytes that survived by scavenging the waste products of eukaryotic cells. Over time mitochondria took up residence in the cell and became true symbionts, but many of their molecular signatures remained those of bacteria.

"Mechanical trauma disrupts cells, so we hypothesized that injury might be releasing mitochondria and their DAMPs into the circulatory system, activating immunity in the same way that infections do when they release PAMPS," explains Hauser.

To test this hypothesis, the investigators first assayed mitochondrial DNA (mtDNA) from blood samples obtained from a large group of patients who had suffered multiple trauma. As predicted, they found that mtDNA levels were increased but surprisingly, they found that levels were often thousands-of-fold above normal levels.

Through a series of subsequent experiments, the researchers showed that mitochondrial peptides acted as classical G-protein coupled

chemoattractants, activating white blood cells through the FPR1 receptor (a receptor that normally senses bacterial proteins) and associated downstream kinases. They similarly showed that mtDNA activates white blood cells through the PRR known as toll-like receptor 9 (TLR9 normally senses bacterial DNA) and its downstream kinases. Interaction of these two DAMPs and their PRRs work synergistically to activate neutrophils. The investigators also found that injection of mitochondria into rats caused peritonitis and reproduced the pulmonary and hepatic inflammation typical of traumatic SIRS.

"This study suggests that mitochondria - which can spill into the bloodstream following a physical injury -- look enough like the bacteria they originated from to elicit an immune response," notes Scott Somers, PhD, program director at the National Institute of General Medical Sciences. "This work offers important insight into why the body's response to physical trauma mirrors that of bacterial sepsis, and may lead to new strategies for treating severely injured patients."

Adds Hauser, "Since external injuries and events causing sterile tissue death seem to have just as much potential for causing SIRS as does infection, many of the conditions that we've traditionally treated with antibiotics may turn out to not be infections and may, in fact, require very different types of treatment. Going forward, we hope to collaborate with researchers who are working to identify the origins of inflammation in other clinical conditions."

Provided by Beth Israel Deaconess Medical Center