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Restoring appropriate movement to immune cells may save seriously burned patients

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Advances in emergency medicine and trauma surgery have had a significant impact on survival of patients in the days immediately after major injuries, including burns. Patients who survive the immediate aftermath of their injuries now are at greatest risk from infections – particularly the overwhelming, life-threatening immune reaction known as sepsis – or from inflammation-induced multiorgan failure. Now, a device developed by Massachusetts General Hospital (MGH) investigators that measures the movement of key immune cells may help determine which patients are at greatest risk for complications, and a novel treatment that directly addresses the cause of such complications could prevent many associated deaths.

"One in every three patients with burn injuries that dies in an intensive care unit does so because of septic complications," says Daniel Irimia, MD, PhD, of the MGH Department of Surgery, corresponding author of a report in the June *FASEB Journal*. "In the days immediately after injury, white blood cells called neutrophils can lose their ability to move to the site of an injury. In an animal model of burn injury, we found that death due to septic complications can be prevented by a treatment that restores the proper movement of neutrophils."

The most abundant type of white blood cell, neutrophils are part of the innate immune system and the body's first line of defense against infections. Normally, neutrophils are drawn towards the site of a infection by chemical signals from bacteria or injured cells. However, it has recently been discovered that – in patients with serious burn injuries

– neutrophils' ability to follow these signals becomes impaired soon after the injury. Not only does that impairment reduce the availability of the cells to fight infection at the site of injury, but misguided neutrophils also can attack healthy tissue, contributing to organ failure. The current study was designed to analyze changes in the speed and direction of neutrophil movement after burn injury and to investigate whether recently identified molecules called resolvins, which normally act to terminate the inflammatory process after an infection has cleared, could also restore normal neutrophil motion after burns.

Using a microfluidic device that measures neutrophil movement developed at the MGH BioMEMS Resource Center, the investigators first confirmed that the ability of neutrophils from burn-injured rats to move towards a chemical signal of injury progressively deteriorates – in both speed and accuracy – as time passes. While cells from uninjured animals moved quickly and directly through a series of microchannels towards the injury signal, cells from blood samples taken 9 days after the injury became trapped in the device or reversed direction. The researchers then showed that application of resolvin D2 significantly improved the in vitro migratory ability of neutrophils from burned animals.

Experiments in living rats revealed that treatment with resolvin D2 restored appropriate neutrophil motion, an effect that lasted at least two days after treatment ended. In addition, when burn-injured animals were subjected to a second sepsis-inducing injury, treatment with resolvin D2 significantly increased survival. For example, in a group of rats injected with a bacterial toxin nine days after a burn injury, all of those pre-treated with resolvin survived, while all untreated animals died.

"Our ability to measure neutrophil movement in great detail gave us the information we needed to develop the optimal dosage and duration of resolvin treatment for the burned rats. Our results also indicate that

neutrophil motility could be a useful biomarker for the actual risk of septic complications in patients," says Irimia, an assistant professor of Surgery at Harvard Medical School who is also affiliated with Shriner's Hospital for Children. "Our experiments in the animal model suggest that a resolvin-based treatment could prevent those complications by restoring the body's own resources, allowing it to respond to secondary infections, which could save hundreds of patients with burns every year. "

Provided by Massachusetts General Hospital