

Research could lead to way to halt deadly immune response

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Researchers have teased out the molecular process that can shut down a marauding, often deadly immune response that kills thousands each year who suffer battlefield casualties, heart attacks, strokes, automobile accidents and oxygen deprivation, according to an article published in the January edition of *Molecular Immunology*.

The article provides additional detail about the enormously complex biomechanics of a reaction first observed in the lab by Neel Krishna, Ph.D., and Kenji Cunnion, M.D., while conducting pediatric research at Children's Hospital of The King's Daughters (CHKD) and Eastern Virginia Medical School (EVMS) in Norfolk, Va.

"Military medics and ER doctors know that one of the most common killers is an out-of-control immune system that destroys organs after a patient who has suffered a trauma is ostensibly stabilized," said Krishna, a pediatric virologist at CHKD and assistant professor of microbiology and [molecular cell biology](#) at EVMS.

The January publication comes almost four years after the two researchers made a serendipitous and unexpected finding when they inserted a shell of a virus that causes childhood diarrhea into a [Petri dish](#) primed to measure the response of primordial immune system.

The complement reaction completely stopped.

"Stopping this reaction pharmacologically could save lives on the

battlefield, in hospital emergency rooms and in neonatal intensive care centers, where doctors struggle to save oxygen-deprived newborns," said Krishna. "Temporarily stopping the response could have a huge impact in trauma and save many lives."

Over the last four years, Krishna and Cunnion have successfully teased out the precise [biological mechanism](#) behind this unexpected response and identified the specific molecular region of the viral shell that stops the complement process.

One of the oldest biological mechanisms in the evolution of life, the complement system is so complex that research scientists spend entire careers studying it, publishing in journals devoted solely to the study of this primordial defense mechanism.

The complement system exists in almost identical form in everything from seagulls to starfish. Its job is to launch a massive, multi-pronged attack against any foreign body that could threaten the life or health of an organism. Each method of attack is instigated by molecular changes involving as many as 30 substances that result in the same effect, a component designed to destroy the membrane encasing offending cells.

In the case of trauma that leaves cells without oxygen for too long, the complement system kicks in when the re-oxygenation occurs and lays waste to partially damaged cells that might otherwise survive. This is known as a reperfusion injury. This process kills slowly, often over several days. In heart attacks, the death of heart cells, cardiomyocytes, during reperfusion is irreversible and lethal. In cases of trauma and hypoxia, the progressive death of brain cells often results in catastrophic, irreversible brain injury or death. Multiple organ dysfunction syndrome caused by reperfusion injury is the leading cause of death in surgical patients and in trauma patients who survive the first 24 hours.

For decades, researchers have worked to develop medications and treatments to mitigate the effects of reperfusion injury.

Stopping the complement cascade could eliminate the major cause. In earlier published research, authors showed that the introduction of the harmless membrane of the coat of human astrovirus, which causes pediatric diarrhea, shuts down the main pathway leading to activation of an often lethal complement cascade. The research published in January's [Molecular Immunology](#), demonstrates that the introduction of the astrovirus shell also shuts down a second major trigger, dubbed the lectin pathway.

"This research explains the almost complete cessation of complement activity," Krishna said. "This rapid cessation can virtually eliminate most reperfusion injuries."

This research expands upon findings presented in September 2009 at the 12th European Meeting on Complement in Human Disease. That presentation drew enthusiastic response from a number of renowned complementologists who sought samples of the astrovirus shard used by Krishna and who intend to launch additional research into the phenomenon.

"We're rapidly moving toward therapeutic application," Krishna said.

Provided by Eastern Virginia Medical School

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