Piece from childhood virus may save soldiers' lives

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A harmless shard from the shell of a common childhood virus may halt a biological process that kills a significant percentage of battlefield casualties, heart attack victims and oxygen-deprived newborns, according to research presented Sunday, September 6, 2009, at the 12th European meeting on complement in human disease in Budapest, Hungary.

Introducing the virus's shell in vitro shuts down what's known as the complement response, a primordial part of the immune system that attacks and destroys the organs and vascular lining of people who have been deprived of oxygen for prolonged periods, according to researchers at Children's Hospital of The King's Daughters (CHKD) and Eastern Virginia Medical School (EVMS), in Norfolk, Va.

The complement response kicks in after the victim has been revived, in what is known as a reperfusion injury. It does its work slowly but unrelentingly, killing soldiers, infants or heart attack victims over the course of days.

"To find a way to manipulate the complement system pharmacologically has been like a search for the Holy Grail," said one of the lead researchers, Dr. Kenji Cunnion, an infectious disease physician at CHKD and an associate professor of pediatrics at EVMS.

While Cunnion and Neel Krishna, Ph.D., a pediatric virologist at CHKD and assistant professor of microbiology at EVMS, focus on pediatric

research, they see clear military applications.

"The complement reaction is one of the major causes of death of the battlefield," said Krishna. "By the time you get a victim to the hospital, it may be too late."

Dr. L.D. Britt, M.D., MPH, Brickhouse professor and chairman of surgery at EVMS, agrees.

"Hemorrhagic shock is the leading cause of death in combat trauma and reperfusion injury plays a significant role both in increased mortality and increased brain damage," said Britt, senior consultant to the military on combat trauma. "This research could help save the lives of soldiers, as well as the lives of other trauma victims who have been without oxygen for extended periods."

Britt has joined Cunnion in Krishna in seeking a grant from the Department of Defense to expedite research and development.

The complement system ranks as one of the oldest biological mechanisms in life's evolution and exists in almost identical form in everything from seagulls to starfish.

Essentially, the complement system recognizes and destroys potentially toxic substances that gain entry into an organism's bloodstream. When a starfish loses a limb, for instance, the complement system sends a contingent of killer cells to block and attack anything that tries to work its way inside.

In human evolution, complement provided an essential natural defense.

"Up until 100 years ago, the vast majority of humans died from infectious diseases," said Cunnion. "Nobody died of old age and almost

nobody lived long enough to die of a heart attack."

Thanks to modern medicine, people now live long enough to die from trauma, such as car accidents, or from conditions, such as heart attack and stroke, that can leave cells throughout the body starved for oxygen. Cells deprived of oxygen often undergo biochemical changes, essentially marking themselves for death. When blood flow and oxygen are restored, these changes trigger the complement cascade. The marauding cells unleashed by complement cascade are indiscriminate, killing not only the cell with the biochemical marker but innocent bystander cells as well.

"It's like throwing a grenade," said Krishna.

A patient, who has suffered survivable brain damage from oxygen deprivation, might die over several days as swaths of cells are destroyed by this seemingly unstoppable reaction. Animal research has shown that stopping this complement reaction significantly reduces brain damage.

The complement system is so complex that research scientists spend entire careers studying it, publishing in journals that specialize in this primordial defense mechanism.

In the case of Cunnion and Krishna, discovering how to shut down the complement system resulted from happenstance. As they worked in neighboring labs, they noticed a similarity in the structure of molecules Cunnion used in his experiments and the protein shell of the astrovirus Krishna studied. They wondered what would happen if they introduced the astrovirus shell into an assay routinely used in Cunnion's lab to assess complement activation.

"It was kind of a shot in the dark," Krishna said. "We didn't expect anything to happen."

The complement reaction completely stopped.

More information: The presentation in Hungary, "Human Astrovirus Coat Protein Binds C1q and MBL and Inhibits the Classical and Lectin Pathways of Complement Activation," highlights not only the discovery, but research published in *Current Topics in Complement II* and the *Journal of Virology*, describing precisely how this tiny piece of protein halts the complement cascade in its tracks.

Source: Eastern Virginia Medical School