Researchers closer to development of drug to prevent deadly immune response

August 26 2010

Researchers have isolated a molecule, small enough to be used as a drug, that can shut down a dysfunctional immune response that causes deadly hemorrhagic shock, results in delayed death of heart attack patients, promotes rejection of transplanted organs and destroys joints in patients with rheumatoid arthritis, according to a paper published in *Molecular Immunology*.

The molecule, a modified peptide, was extracted from the relatively huge protein shell of a common virus that is a frequent cause of childhood diarrhea, according to the research conducted by a team at Eastern Virginia Medical School and Children's Hospital of The King's Daughters.

The discovery marks a quantum leap toward clinical application by creating a powerful effect with a molecule small enough to be used in medications.

"This puts us in a position to move rapidly from in-vitro testing to in-vivo testing," says Neel Krishna, PhD, an assistant professor of microbiology and molecular cell biology at EVMS and a pediatric virologist at CHKD.

The publication comes almost five years after Dr. Krishna and Kenji Cunnion, MD, an associate professor of pediatrics at EVMS and an infectious disease specialist with Children's Specialty Group at CHKD, inserted a shell of a virus that causes childhood diarrhea into a Petri dish

primed to measure the response of a primordial component of the human immune response known as the complement system.

The complement reaction completely stopped.

"Being able to pharmacologically modulate the complement system could have a huge impact on the practice of medicine, potentially saving the lives of victims of hemorrhagic shock, heart attack patients, and even infants who have suffered prolonged hypoxia," says Dr. Krishna. "It could also have a significant impact on treating a wide range of autoimmune and inflammatory diseases."

The complement system is one of the oldest surviving remnants of the earliest life forms and exists in almost identical from in everything from seagulls to starfish.

It developed during millions of years in which the deadliest threat to all life forms, including humans, was not car accidents, heart attacks or the rejection of transplanted organs but infectious disease.

A complex cascade of dozens of biochemical reactions is designed to launch an attack that destroys the membranes of cells damaged by infection.

After trauma has left cells without oxygen for too long, the complement system kicks in when oxygen returns and lays waste to damaged cells that might otherwise survive. This is known as a reperfusion injury, and in some case occurs over a series of days.

In heart attacks, the death of heart cells during reperfusion can be irreversible and lethal. 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.

The inflammatory response also plays a major role in autoimmune and inflammatory diseases such as rheumatoid arthritis.

In earlier published research, the authors showed that the introduction of the harmless protein shell that encases the astrovirus, which causes pediatric diarrhea, shuts down two of the three methods used by the complement system to destroy damaged cells, but doesn't interfere with the part of complement reaction that can offer protection from invading pathogens.

The molecule that modulated the complement cascade, however, was relatively large, consisting of 787 amino acids, too sizable to be used therapeutically.

By meticulously testing smaller shards of the shell, researchers found and then modified a shard consisting of just 30 amino acids that actually was more effective than the larger molecule. That smaller segment, a modified peptide dubbed E23A, makes it a viable candidate for in-vitro testing of the compound.

"In-vitro testing is a significant step toward developing a drug that can be used therapeutically," says Dr. Krishna.

More information: Paper: doi:10.1016/j.molimm.2010.07.012

Provided by Eastern Virginia Medical School

Citation: Researchers closer to development of drug to prevent deadly immune response (2010, August 26) retrieved 26 April 2024 from https://medicalxpress.com/news/2010-08-closer-drug-deadly-immune-response.html

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