

Penn Medicine News

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Action of Modern Drug Demonstrates How Two Ancient Human Systems Interact, Penn Study Finds

Implications for Reducing Clotting in Kidney Disease Dialysis and Sepsis

PHILADELPHIA –The interaction of the drug compstatin with two ancient, co-evolved human systems points to new ways for reducing clotting during dialysis for end-stage kidney disease and multiple organ failure due to sepsis, a dangerous whole-body inflammatory response to infection.

“It has been suspected, but not demonstrated in vivo, until now, that these two systems are able to interact,” says study author [John D. Lambris, PhD](#), the Dr. Ralph and Sallie Weaver Professor of Research Medicine at the [University of Pennsylvania School of Medicine](#). “Our basic research on these two human systems is helping us to come up with new ways to stop clotting problems.”

One system, called complement, an evolutionarily old arm of the immune system, comprises a network of proteins that “complement” the work of antibodies in destroying foreign invaders. The system serves as a rapid defense mechanism in most species from primitive sponges to humans.

The second system, coagulation, or blood-clotting, is also evolutionarily old and co-evolved with the complement system.

Penn researchers, along with an international team of collaborators, describe that inhibition of the complement system using compstatin helps to stop clotting problems during dialysis and in cases of sepsis, according to two recent articles published online in *Blood*.

Compstatin is a small molecule designed to specifically and maximally inhibit the complement harmful reactions by attaching to a complement molecule called C3.

Reaction to Dialysis Materials

Complement activation is often triggered by the tubing and filters used during dialysis itself, causing problems with blood clotting. However, the mechanism by which long-term dialysis causes clotting has not been clear. In the U.S. more than 500,000 receive treatment for end-stage renal disease annually.

In recent years, the adverse effects of dialysis have become a serious health and economic problem nationwide: The number of patients with end-stage renal disease has been steadily increasing in the U.S. over the past few decades, at a rate of approximately 9 percent per year, the highest increase in any developed country.

To solve this problem, Lambris reasoned that if the complement system was involved in triggering blood clotting, then inhibition of complement by compstatin binding to C3 would also stop the clotting. "We found that materials used in dialysis trigger the complement system and that the generation of certain complement molecules results in the expression of active tissue factor, a key initiator of clotting," said Lambris. The Penn group found that compstatin blocks the generation of the complement molecules C5a, which stimulates the release of tissue factor from neutrophils.

These findings suggest that compstatin, or other drugs that target the complement system, might be therapeutic agents to prevent clotting in patients with renal failure who are maintained on long-term dialysis.

Staying Sepsis

During severe sepsis, which accounts for about 210,000 deaths annually in the US, the complement system is part of the primary response to an invading pathogen. However, both the complement and the coagulation systems can work overtime during sepsis, leading to multiple organ failure and death.

In a baboon model of severe sepsis caused by a sub-lethal dose of *E. coli*, Lambris and colleagues found that treating the animals with compstatin during the acute or secondary phase of sepsis reduced both blood and tissue markers of complement activation and blood coagulation.

"Similar to the dialysis study, this shows that there is an interplay between the complement and coagulation systems," said Lambris.

Blocking the interplay between the two systems by compstatin, or a similar drug, may become a therapeutic strategy to prevent the devastating effects of sepsis.

"We are investigating several compstatin-related compounds that are one thousand times more active than compstatin, which was discovered in our lab 13 years ago," said Lambris. Toxicity studies will be required before these newer compounds can move into human trials.

The Penn studies were done in collaboration with researchers at the Democritus University of Thrace, Greece; the University of Oslo, Sweden; the Oklahoma Medical Research Foundation; and the Oklahoma University.

These studies were supported by grants from the [National Institute of Allergy and Infectious Diseases](#); the [National Institute of General Medical Sciences](#); and the [National Institute of Biomedical Imaging and Bioengineering](#).

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