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Immune compound blocks virus' ability to hijack antibodies

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Researchers at Washington University School of Medicine in St. Louis have shown that a controversial phenomenon known as antibody-dependent enhancement (ADE) of infection is suppressed by C1q, a blood-borne immune system compound.

The link may give researchers the lead they need to begin untangling a snarl of evidence from decades of puzzling epidemiological and laboratory-based studies of ADE. Better understanding of ADE will help public health experts and clinicians working to control some viral disease outbreaks and aid efforts to design safe and effective vaccines.

ADE reverses the conventional picture of immune resistance to disease, which says victory over an invader leaves the body better prepared to fight the invader if it returns. In the 1960s, though, epidemiological studies of dengue fever virus infections showed that patients who had beaten the virus once could be more vulnerable to it when they became infected again with a related but not identical strain.

Scientists theorized that the vulnerable patients didn't have adequate antibodies to eradicate the dengue virus when it returned, and that as a result the virus was somehow taking advantage of the antibodies and using them to accelerate infection. The theory was based on evidence from experiments in cell cultures, where adding virus to blood serum with low levels of antibodies led to higher viral replication levels. However, when researchers tried to simulate the phenomenon in animal models, they could not.

"In theory, this should be a very easy model to make," says senior author Michael Diamond, M.D., Ph.D., associate professor of molecular microbiology, of pathology and immunology and of medicine. "Part of the problem has been a lack of good animal models of dengue infection, but cell culture studies have suggested ADE also may play a role in other types of viral infection. And yet we still have had only three partially successful animal models of ADE, and that had some people suggesting that maybe ADE only happens in cell cultures, not in whole organisms."

One major problem, Diamond and his colleagues report this week in *Cell Host & Microbe*, was that cell culture experiments had unknowingly used blood sera where a key immune compound, C1q, had broken down or was at inadequate concentrations.

"We started by noting that the epidemiological data on ADE suggest it happens only very rarely," Diamond explains. "That made us wonder: why is it so rare if you can make it happen in a lab dish so easily? Is something important missing in the cell culture experiments that can suppress ADE?"

Researchers began their search for a potential missing suppressor in the complement system, a family of immune compounds that normally circulate in the bloodstream. When the immune system detects an invader, it can activate these compounds, transforming them into inhibitors against the invader. But unless blood sera are carefully procured, processed and stored, complement proteins break down very easily.

Exposure to heat, for example, breaks down complement. So researchers conducted an ADE test, but instead of using stored blood sera, they took fresh sera from mice and applied it to dengue virus and therapeutic antibodies for dengue. Fresh, unheated sera blocked ADE; heated sera, which lacks complement, did not.

Scientists next tested sera from several different lines of mice, each genetically engineered to be missing one component of complement. Only sera from mice missing C1q led to ADE in cell cultures. When they added purified C1q to virus and antibodies, it blocked ADE.

Although they have now firmly linked C1q to ADE suppression, the researchers found evidence in follow-up experiments that other immune factors also affect the chances that ADE will occur. An initial attempt by Diamond's lab to simulate ADE in a mouse model of West Nile virus infection, for example, had limited success. But he and his colleagues are hopeful that C1q is the lead they need to begin assembling a complete picture of what happens in ADE and to potentially one day open the door to the development of therapeutic or preventive treatments.

Source: Washington University School of Medicine