Scientists find promising vaccine targets on hepatitis C virus

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A team led by scientists at The Scripps Research Institute has found antibodies that can prevent infection from widely differing strains of hepatitis C virus (HCV) in cell culture and animal models.

HCV's very high rate of mutation normally helps it to evade its host's immune system. The newly discovered antibodies, however, attach to sites on the viral envelope that seldom mutate. One of the new antibodies, AR4A, shows broader HCV neutralizing activity than any previously reported anti-HCV antibody.

"These antibodies attach to sites on the viral envelope that were previously unknown, but now represent promising targets for an HCV vaccine," said Mansun Law, an assistant professor at Scripps Research. Law is the senior author of the new report, which appears online this week in the Proceedings of the National Academy of Sciences.

An effective HCV vaccine is desperately needed. The World Health Organization (WHO) estimates that the virus has established mostly silent infections in 130 to 170 million people worldwide—nearly 3 percent of the human population—and spreads to 3 to 4 million new people annually. HCV principally infects liver cells, and is thought to cause chronic, often-unnoticed liver inflammation, which eventually can lead to serious liver ailments. The virus already is responsible for about a quarter of annual US cases of liver cirrhosis and primary liver cancer, and it is the leading cause of liver transplants. In some developing countries, HCV prevalence is extremely high; studies suggest that in

Egypt, as many as 22 percent of the population is infected—apparently due to poor screening of blood products and past re-use of syringes. Even in developed countries, HCV infections represent a looming public health crisis. In the United States and Europe, up to 14 million people are now HCV-positive, and each year an estimated 150,000 people are newly infected.

The current leading treatment for HCV infection involves a 12- to 36-week course of the immune-stimulating protein interferon-alpha, the antiviral drug ribavirin and HCV protease blocker. But it is not completely effective, and it causes significant adverse side effects—aside from being very expensive. To fully stamp out the HCV pandemic, especially in developing countries, scientists will have to develop a cheap preventive vaccine.

Yet an effective HCV vaccine has so far been elusive. The virus mutates very rapidly, and thus, antibodies raised against one isolate of HCV typically won't protect against a subsequent HCV infection. Hospital samples of HCV suggest that the virus's genes, and the proteins for which they code, are highly variable even within an individual patient.

"One of the big goals of HCV vaccine development has been to find an accessible spot on the virus that doesn't change constantly," said Law.

To find such vulnerable spots, researchers sift through antibodies sampled from infected people and look for those antibodies that can neutralize a broad range of viral strains. The locations on the virus where those broadly neutralizing antibodies bind mark the vulnerable viral structures that can be used as the bases of a broadly effective, antibody-stimulating vaccine. Previous studies, including a 2008 study in *Nature Medicine*, for which Law was lead author, have found some broadly neutralizing HCV antibodies. But for the present study, Law and his colleagues used a more thorough approach, known as "exhaustive

panning," to see if they could find new and even more broadly neutralizing antibodies. "Exhaustive panning is a powerful technique for finding rare antibodies that might otherwise go undetected," Law said.

HCV employs a complex of two envelope glycoproteins, E1 and E2, to grab and fuse with target cells. Erick Giang, a research assistant in Law's lab, harvested this viral E1-E2 complex from HCV-producing cells in a lab dish and used it as "bait" for a panel of antibodies derived from the blood of a person with chronic HCV infection. The exhaustive panning technique involves exposing this bait protein to different anti-HCV antibodies in sequence, so that the known antibody-binding sites on the complex are progressively covered until only new ones are left.

In this way, Giang catalogued 73 new anti-HCV antibodies, which bind to five distinct "antigenic regions" on the E1-E2 complex. In standard cell culture tests of HCV-neutralizing ability, several of these antibodies showed an ability to neutralize infection by a wide range of HCV strains. One, AR4A, turned out to bind to an almost-unvarying spot on E1-E2 complex, close to the surface of the virus's outer coat of fat molecules. AR4A showed significant neutralizing ability against all 22 HCV strains in a test panel—not only in tests in Law's lab, but also in confirmatory tests at the University of Copenhagen.

The new antibody thus is more broadly protective than the previous top contender, AR3A, which Law described in his 2008 *Nature Medicine* paper. "This human antibody AR4A has the broadest HCV-neutralizing activity known to the field," Law said.

Collaborating researchers at Rockefeller University, who recently engineered a line of HCV-infectable mice, showed that AR4A antibodies protected these mice from two widely different HCV strains. A combination of half-doses of AR3A and AR4A antibodies worked less well.

The next step for Law and his colleagues is to start making and testing prototype vaccines based on the vulnerable HCV binding sites that have been revealed by these antibody studies. The researchers also plan to use the new antibodies to study the structure and function of HCV proteins such as the all-important E1-E2 complex.

Anti-HCV antibodies such as AR4A and AR3A could have some therapeutic use, too. Although they wouldn't be able to clear existing HCV infections and would be too expensive and difficult to use on a large population to prevent new infections, they could be useful in preventing new HCV liver infections in liver transplant patients. Such infections can spread from HCV reservoirs in the patient's body to the newly transplanted liver tissue.

"Antibody-based treatment has worked extremely well for liver transplants to patients with hepatitis B virus, and we hope the new HCV antibodies can be just as helpful to HCV liver transplant patients," Law said.

More information: "Human broadly neutralizing antibodies to the envelope glycoprotein complex of hepatitis C virus," *Proceedings of the National Academy of Sciences.*

Provided by The Scripps Research Institute