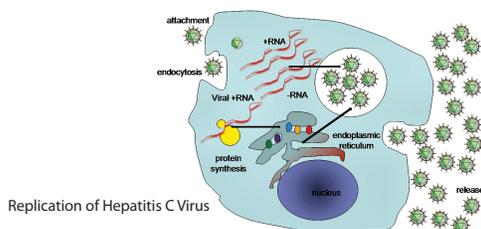




A Potential Strategy for Successful Treatment and Prevention of Hepatitis C Infection

Antibodies that interfere with neutralizing antibodies against hepatitis C virus were identified; eliminating them might be the key to better treatments and an effective vaccine



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Depletion of interfering antibodies in chronic hepatitis C patients and vaccinated chimpanzees reveals broad cross-genotype neutralizing activity

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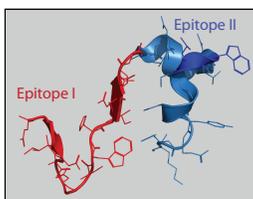
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Hepatitis C Virus: Silent Infection and Major Global Health Issue

About 170 million people worldwide are infected with hepatitis C virus (HCV), including 4 million in the US. More than 70% of individuals infected with HCV fail to clear the virus from their body, even though they make neutralizing antibodies that bind to the virus and prevent it from infecting cells. About 20% of these chronically infected individuals subsequently develop cirrhosis, which can lead to liver cancer. HCV-associated cirrhosis is the leading indication for liver transplantation in the US. The current antiviral drug therapy is arduous, and fails in about half of the cases. Preparations of antibodies manufactured from anti-HCV-positive plasma (HCIGIV) fail to reduce HCV levels or prevent a repeat infection after liver transplantation. One of the obstacles to preventing HCV infection has been the lack of understanding of how HCV infection persists despite the presence of neutralizing antibodies.

Immunological Interference in Hepatitis C Infection

A team of FDA/CBER researchers and their colleagues at the National Institutes of Health previously discovered that the E2 protein (an antibody-generating target, i.e., antigen on the surface of HCV) comprises two adjoining sections, Epitope I and Epitope II. Antibodies to Epitope I neutralize HCV, but antibodies to Epitope II are ineffective, i.e., non-neutralizing. Moreover, when the non-neutralizing antibodies bind to Epitope II they interfere with the neutralizing antibodies against Epitope I.

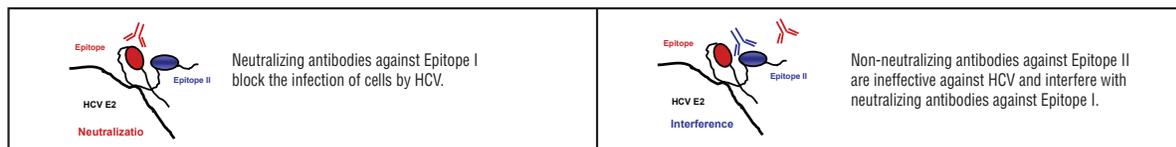


Model of Hepatitis C Virus Epitopes I and II

Depleting the Interfering Antibodies

The discovery of interfering (non-neutralizing) antibodies against Epitope II suggests that this is the reason HCV infection can persist even in the presence of an abundance of neutralizing antibodies against Epitope I.

CBER and NIH researchers tested that hypothesis by using plasma containing antibodies to Epitopes I and II from a chronically HCV-infected patient and from chimpanzees immunized to produce antibodies against both of these epitopes. Plasma containing both types of antibody did not neutralize HCV. However, when the researchers trapped and removed the non-neutralizing antibodies from the plasma, the remaining antibodies neutralized HCV. This finding is especially important because Epitope II is variable, that is, it mutates readily. But since Epitope I is constant, antibodies originally made against one subtype of HCV will bind a broad array of subtypes of the hepatitis C virus.



Turning Discoveries into New Treatments

These new insights into neutralizing and interfering antibodies to HCV Epitopes I and II are the basis of new research at CBER aimed at improving HCIGIV and developing a safe and effective vaccine against the virus. CBER researchers are continuing to evaluate whether depleting interfering antibodies from HCIGIV would enhance its ability to neutralize HCV and prevent the virus from infecting cells. In addition, it might be possible to develop an effective vaccine by preserving the amino acids in Epitope I responsible for triggering production of neutralizing antibodies, while preventing production of interfering antibodies by mutating amino acids in Epitope II that are responsible for triggering the production of non-neutralizing antibodies by the immune system.

CBER research has laid the foundation for development of hepatitis C infection prevention strategies that could significantly reduce illness and medical costs.