New model for hepatitis B helps identify potential new therapeutic approach

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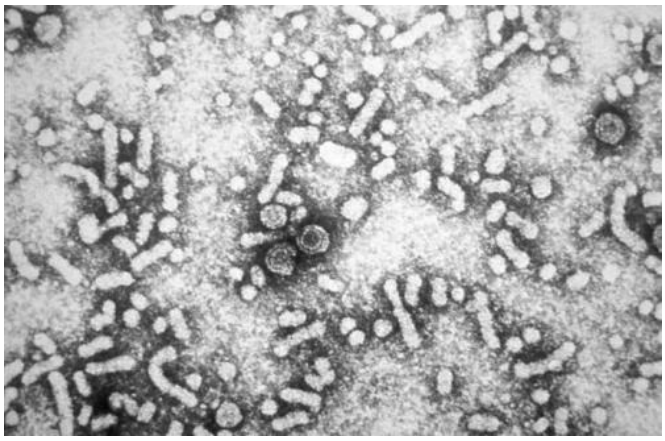

Electron micrograph of hepatitis B virus. Credit: Centers for Disease Control and Prevention

A promising new avenue for treating hepatitis B has been reported by researchers at Hiroshima University who have developed a new animal model of the disease.

About two million people worldwide have been exposed to hepatitis B virus. Liver transplantation is often necessary to save the lives of patients who have severe liver damage that results from acute overreaction of the immune system. To develop therapies against acute hepatitis, an appropriate animal model is necessary. "The number of patients who can receive liver transplantation is limited, so there is an urgent need to develop new treatment options," said Professor Kazuaki Chayama.

Professor Chayama and his research group used mice with "humanized" livers, and injected them with human blood. They found that hepatitis in these "human hepatocyte chimeric mice" was caused by white blood cells known as cytotoxic T lymphocytes (CTLs) that were specifically targeted to hepatitis B virus. This was very similar to human acute hepatitis B.

The researchers also found that treating the mice with a molecule called CTL-associated antigen-4 immunoglobulin (CTLA4Ig) suppressed damage to liver cells infected with hepatitis B virus, suggesting that this might be a potential approach to treatment. The mouse model should also be useful for studying the immunological reactions and viral clearance in hepatitis B virus infection, they note in the *Journal of Virology*.

In this study, the Hiroshima University researchers developed an animal model using severely immunodeficient mice whose livers were partially populated with human cells, in order to reconstruct elements of the human immune system.

"After we inoculated the mice with hepatitis B virus, we injected them with human peripheral blood mononuclear cells and then with CTLA4Ig," Professor Chayama said.

"Injecting the human blood cells resulted in massive liver cell damage and we were able to detect cytotoxic T lymphocytes that specifically targeted hepatitis B virus in liver infiltration cells. The presence of these lymphocytes is thought to be necessary in acute liver inflammation," he said. "CTLA4Ig treatment dramatically inhibited this infiltration."

Because the researchers found that CTLA4Ig was effective in suppressing hepatitis in this study, they suggest that CTLA4Ig should be among the therapeutic options investigated further as a potential therapy for patients with severe acute hepatitis B. To this end, this animal model is useful for virological and immunological analysis of HBV infection.

More information: Takuro Uchida et al. Human Cytotoxic T Lymphocyte-Mediated Acute Liver Failure and Rescue by Immunoglobulin in Human

Hepatocyte Transplant TK-NOG Mice, *Journal of Virology* (2015). DOI: 10.1128/JVI.01126-15

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