Hepatitis B: Natural controllers shed light on immunity mechanisms

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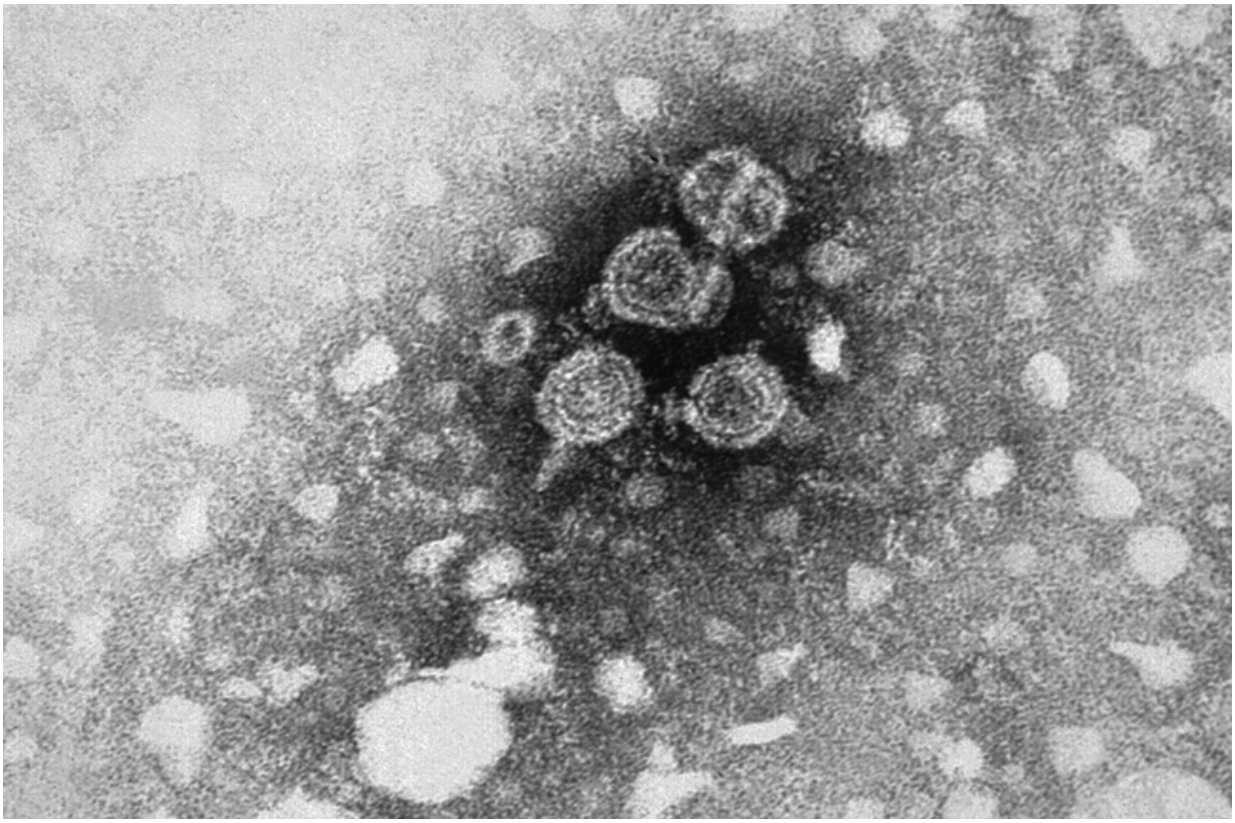

A microscopic image of the Hepatitis B virus, taken by the Centers for Disease Control and Prevention

Infections in humans caused by the hepatitis B virus (HBV) represent a major public health problem. Despite the availability of effective

protective vaccines, more than 250 million individuals worldwide are chronically infected according to WHO estimates. HBV infection is associated with cirrhosis, liver failure and hepatocellular carcinoma, responsible for approximately a million deaths every year. To date there is no specific treatment to completely eliminate the virus and provide a cure for chronic HBV infection. Strikingly, however, about 1% of individuals with chronic HBV infection, known as natural controllers, are capable of recovering spontaneously. To improve our understanding of the antibody response conferring protection against HBV infection, scientists from the Institut Pasteur and Inserm, in collaboration with the Roche Innovation Center in Switzerland, produced and characterized human monoclonal antibodies specific to viral envelope antigens, referred as HBsAg, from blood memory B cells isolated from HBV vaccinees and natural controllers.

Hepatitis B is one of the major human diseases: it is estimated that 2 billion people have been infected with the virus and more than 250 million are chronic carriers capable of transmitting the virus over many years. Chronic carriers are exposed to a high risk of death from liver cirrhosis or liver cancer, diseases that claim around a million lives every year (see our fact sheet).

There are no drugs available to treat acute hepatitis and improve the chances of recovery. But some rare patients, known as natural controllers, undergo seroconversion—they develop antibodies against the virus that can be detected in the blood, conferring protection against the disease similarly to vaccination. In response to HBV infection, specific antibodies produced by immune cells called B lymphocytes recognize HBsAg, some of which being able to block viral infection (neutralization) and propagation by destroying infected liver cells (hepatocytes). Thus, such antibodies appear to play a crucial role in eliminating HBV and protecting against infection.

New therapeutic avenue for the treatment of hepatitis B virus

To investigate the antibody response involved in the protection against HBV infection and analyze in details the properties of the antibodies directed against the virus, the laboratory of Humoral Immunology (Institut Pasteur / INSERM U1222), in collaboration with the Roche Innovation Center in Switzerland, scientists from the units led by James Di Santo and Pierre Charneau (Institut Pasteur), and the teams led by Stanislas Pol (Cochin Hospital) and Camille Sureau (French Blood Transfusion Institute (INTS)), produced and characterized about a hundred human monoclonal antibodies specific to the HBV surface antigens (HBsAg) expressed by memory B cells isolated from the blood of vaccinees and individuals cured of chronic infection (natural controllers).

"The study shows that vaccinees and natural controllers are capable of generating a wide array of antibodies targeting different regions of HBsAg," explains Hugo Mouquet, head of the Humoral Immunology Laboratory at the Institut Pasteur and investigator for the study. The vast majority of anti-HBsAg antibodies produced in controllers are neutralizing and capable of reacting with different HBV subtypes circulating worldwide. Apart from their neutralizing ability in vitro at low concentrations, the antibody candidates tested in mouse models of HBV infection led in vivo to a substantial drop in viremia—the level of viral particles in the blood for a given virus. Importantly, the passive administration of the broadly neutralizing antibody Bc1.187, isolated from a controller subject, into infected mice led to a drastic decrease of viremia and in some mice, to a long-term post-therapy control of the infection.

"The neutralizing antibodies directed against HBsAg thus appear to play

a key role in the natural control of infection in chronically infected patients," continues Hugo Mouquet. The antibody Bc1.187 represents a highly promising therapeutic tool for the treatment of patients with chronic HBV infection and/or an alternative to the polyclonal immunoglobulins used in some indications to prevent transmission of the virus in humans.

More information: Verena Hehle et al, Potent human broadly neutralizing antibodies to hepatitis B virus from natural controllers, *Journal of Experimental Medicine* (2020). DOI: 10.1084/jem.20200840

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