Checkmate for hepatitis B viruses in the liver

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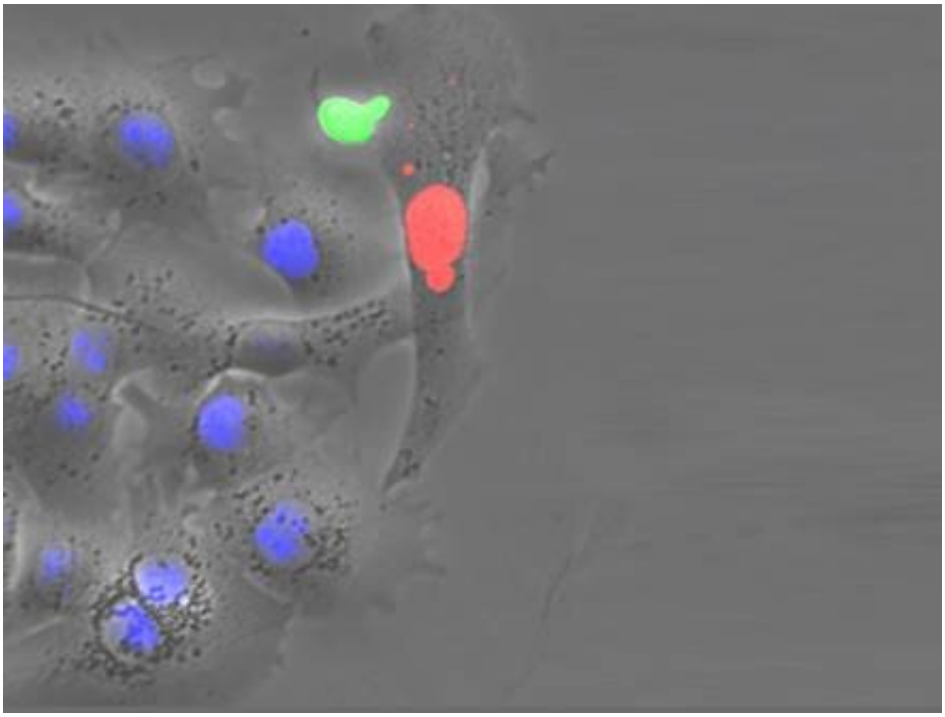

The image shows in a HBV-specific T cell (green) attacking a target cell, in which viral proteins are produced (red) and HBV negative cells (blue). © Helmholtz Zentrum München / Jochen Wettengel

Researchers at Helmholtz Zentrum München and the Technical University of Munich, working in collaboration with researchers at the University Medical Center Hamburg-Eppendorf and the University Hospital Heidelberg, have for the first time succeeded in conquering a chronic infection with the hepatitis B virus in a mouse model. The team showed in its publication, that T-cell therapy can provide a permanent

cure. Up to now it has not been possible to fully control the virus. Their findings have now been published in the *Journal of Clinical Investigation*.

Infections with the hepatitis B virus (HBV) are a global health problem. According to the World Health Organisation (WHO), more than 260 million people worldwide are chronically infected with the virus. Vaccination prevents new HBV infections, but for people who are chronic carriers of the virus, a cure has not yet been found. Available drugs only prevent the virus from continuing to replicate in liver cells, but they cannot eliminate it. In the long term, this can lead to complications such as liver cancer or liver cirrhosis, whereby functional liver tissue is replaced by fibrous connective tissue.

"Currently, chronic hepatitis B cannot be cured. We have now been able to show that T-cell therapy exploiting new technologies presents an encouraging solution for the treatment of chronic HBV infection and liver cancer that is triggered by the virus. That is because these 'living drugs' are the most potent therapy we have at our disposal at present," explains Prof. Ulrike Protzer. She is Director of the Institute of Virology at the Helmholtz Zentrum München and at the Technical University of Munich, both members of the German Center for Infection Research (DZIF).

T cells eliminate hepatitis B

According to Dr. Karin Wisskirchen, first author of the study and scientist in the group of Ulrike Protzer, the new T-cell therapy was specifically developed as an approach to fighting HBV infection and HBV-associated liver cancer. It is known that in chronically infected patients, virus-specific T cells either cannot be detected or they demonstrate decreased activity. However, if patients are able to keep the virus under control by themselves, a strong T-cell response becomes detectable. "The obvious answer is therefore to use virus-specific T cells

to make up for this deficit," Dr. Wisskirchen says. The genetic information for HBV-specific T-cell receptors was obtained from patients with resolved infection. In the laboratory, it can then be introduced into T cells from the blood of patients with chronic hepatitis B. This leads to the formation of new, active T cells, which fight the virus or virus-induced cancer cells. T cells created in this way were able to completely eliminate HBV-infected cells in the cell culture.

In cooperation with the group led by Prof. Maura Dandri, Hamburg the immune cells were then tested in a humanized mouse model. A single dose of the receptor-modified T-cells was sufficient to control the virus in the liver. Hereby, the T-cells only attacked infected liver cells and spared healthy tissue. Myrcludex B, an experimental drug developed by Prof. Stephan Urban, Heidelberg, was then administered to prevent the virus from infecting healthy liver cells again as soon as the T-cells had stopped circulating. As a result, the infection was completely cured.

Preparations for a clinical study

"The promising results of this study will help us to further investigate the potential of T-cell therapy and go ahead with clinical trials along with our partners. We are thus taking a decisive step towards establishing this form of personalized medicine," Prof. Protzer says. Her group will therefore continue to explore ways of applying the therapy to the widest possible group of patients. The Helmholtz Zentrum München has out-licensed parts of its T-cell therapy to SCG Cell therapy Pte. Ltd. "Together with our partner we are planning a clinical trial to study the treatment of patients with HBV-associated hepatocellular carcinoma," Dr. Wisskirchen explains. T-cell therapy is a highly innovative area that has gained momentum thanks to the significant success of clinical trials in the treatment of lymphoma. Prof. Dandri stresses: "Such progress would not be possible without the close cooperation that we have within the German Center for Infection Research."

More information: Karin Wisskirchen et al. T cell receptor grafting allows virological control of hepatitis B virus infection, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI120228