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A new opportunity for hepatitis C research

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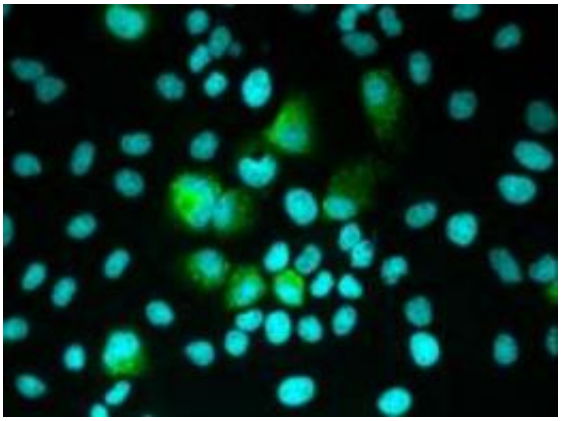

This image shows infected human cells with miceCD81. Credit: Twincore, Hannover, Germany

The hepatitis C virus is highly specialised. We humans are its natural hosts. The only other living organisms that could be infected with the hepatitis C virus in the lab are chimpanzees. Nevertheless it is - from the viewpoint of the virus - highly successful: around 170 million people are chronically infected with the virus. And with the chronic infection the risk of developing liver cancer also increases.

Researchers worldwide are working to develop vaccines and medication to combat the virus. The problem is that although they are able to research in liver cell cultures, when they want to find out how the immune system controls an infection or whether possible vaccines are effective research comes up against a brick wall: tests at such an early stage are unthinkable for humans or chimpanzees.

At TWINCORE researchers are now adapting the HCV to mice, thus enabling immunologists and vaccine researchers to take the next steps against this illness in the future. Because the immune system of mice is very similar to that of humans and it is only when vaccines are successful and safe in animal experiments that researchers can take the risk of transferring them to humans.

The fact that HCV can only infect humans and chimpanzees is partly down to the highly complicated mechanism with which it accesses the cell. The virus has to first bind four different molecules on the surface of our liver cells. This triggers a mechanism in our cells that transports the virus into the liver cells. "Mice also have these receptors on their liver cells in principle," says scientist Julia Bitzegeio of the Department of Experimental Virology at TWINCORE, "however, they do not fit those on the surface of the virus."

The two molecules that cause particular difficulty are called CD81 and occludin - these need to be human, otherwise the virus has no chance of infecting the cell. To make the HCV "mouse-capable" the researchers resorted to a trick: they have removed the CD81 receptor from human liver cells and replaced it with mouse CD81. In an electrical field they then tore tiny holes in the cell membrane before inserting the HC virus artificially through these holes. "The virus reproduced inside the cells and we repeatedly inserted the virus into the altered liver cells," explains Julia Bitzegeio. This led to the highly transformable virus gradually changing until it was able to penetrate the cells with mouse CD81 receptor even without assistance.

"In this selection process the surface of the virus altered so much that it continued to infect human cells very quickly, but also simple mouse cells containing the four mouse variants of the HCV receptors," says Research Group Leader Professor Thomas Pietschmann. The mouse-adapted virus is able to penetrate the mouse cells; however, the human specialisation

of the HC virus is so high that it is unable to reproduce in the cells. "Successful infiltration is the first step towards a new small animal model, one that is urgently required for immunological investigations and the development of vaccines against HCV."

More information: Bitzegeio J, Bankwitz D, Hueging K, Haid S, Brohm C, et al. (2010) Adaptation of Hepatitis C Virus to Mouse CD81 Permits Infection of Mouse Cells in the Absence of Human Entry Factors. PLoS Pathog 6(7): e1000978. doi:10.1371/journal.ppat.1000978