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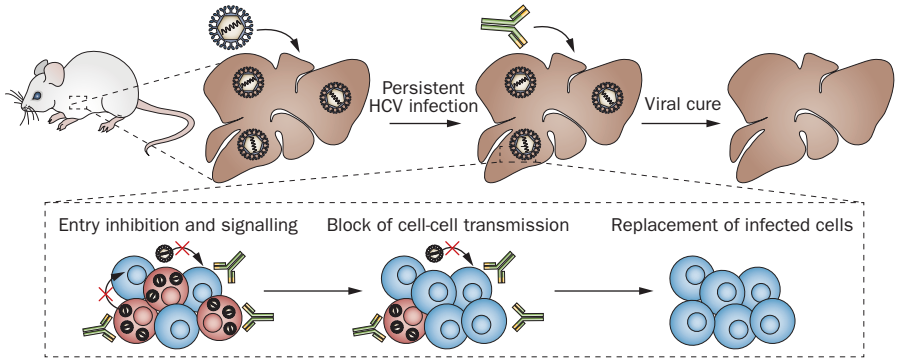
HEPATITIS

Tightening the grip on clearing HCV infection

Targeting a host factor involved in cellular entry of HCV could be a promising new approach in the treatment of HCV infection, according to new research published in *Nature Biotechnology*. A monoclonal antibody (mAb) specific for the tight junction protein claudin-1 (CLDN1) prevented and eliminated chronic HCV infection *in vivo* in a human liver–chimeric mouse model, inhibiting HCV entry, HCV cell-cell transmission and virus-induced signalling events.



Clearance of HCV infection in a humanized mouse model using a CLDN1-targeting mAb. Image developed with T. Baumert.

Direct-acting antiviral agents (DAAs) have revolutionized the treatment of hepatitis C, with remarkable high cure rates using the new combination therapies. "Although we have seen tremendous progress in the development of antivirals, there is a need for novel approaches complementing these DAAs," says author Thomas Baumert, INSERM and University of Strasbourg, France. Previous studies had identified CLDN1 as a key factor that mediates HCV entry into host cells and, crucially, that a CLDN1-specific mAb had antiviral effects in cell culture models. Baumert and colleagues took the next step and tested this mAb *in vivo* in their bid to find alternative treatments for hepatitis C.

The researchers used a humanized mouse model—the human chimeric urokinase-type plasminogen activator-transgenic severe combined immunodeficiency mouse—for their studies as this model supports robust, long-term HCV infection. The CLDN1-specific mAb was tested in several scenarios (*de novo* and chronic HCV infection) and with different HCV strains.

First, the investigators confirmed that short-term administration of the CLDN1-specific mAb prevented *de novo* infection with HCV (genotypes 1b and 4). Successful treatment (four intraperitoneal injections of the mAb in total, one per week) was observed in mice persistently infected with HCV (cell-cultured-derived genotype 2a/2a chimera). Importantly, mice treated with the CLDN1 mAb had undetectable serum levels of HCV RNA after 2–4 injections and remained free of the virus until the end of the study period; however, one mouse did relapse, which the study authors noted was unlikely to be because of the presence of resistant HCV variants and potentially owing to low serum mAb concentrations early in treatment. Antiviral activity of the CLDN1 mAb was also observed against different cell-culture derived or HCV isolates (genotype 1b/2a chimera, 2a and 4).

Next, the safety of the antibody was assessed using a variety of tests, including histopathological analysis of the livers of treated mice, toxicity studies and tests for intestinal paracellular permeability and intestinal transit. Overall, the CLDN1 mAb was found to be safe with no major toxicity or adverse effects reported.

Finally, the researchers examined antiviral mode of action *in vitro* and *in vivo*. The CLDN1-specific mAb inhibited both cell entry (affecting the CD81–CLDN1 co-receptor complex formation) and cell-cell transmission of HCV, as well as virus-induced signalling pathways, particularly EGFR–MAPK signalling. The mAb did not affect HCV replication, assembly or release. These effects ultimately led to the elimination of infected hepatocytes and their replacement with noninfected cells, bringing about viral control and clearance.

"The results are indeed intriguing: not only did the injection of the antibody prevent infection in the experimental animals but, importantly, appeared to control infection after 2–4 injections in persistently infected animals," notes Geoffrey Dusheiko, University College London, UK, who was not involved in the study. Dusheiko postulates that the new approach could have potential for ancillary treatment of hepatitis C, with the CLDN1-targeting mAb proving particularly useful in the setting of transplantation or in patients with advanced liver disease (such as decompensated cirrhosis). "Clinical trials to establish the correct dosing, administrative route and safety of CLDN1-antibodies would be required before such a strategy would be utilized," he cautions, noting that viral clearance was achieved for several HCV strains. Studies for HCV genotype 3 are warranted, which is proving the most difficult variant to treat with the new DAAs.

Baumert and colleagues are hopeful. The researchers aim to move the research into the clinic, with the development of a humanized version of the antibody to be tested for efficacy and safety in patients undergoing liver transplantation for HCV-associated end-stage liver disease or in patients with resistance or nonresponse to the current DAAs. Furthermore, they hope to extend the approach of targeting host entry factors to other viral infections, such as HBV or dengue virus.

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Original article Mailly, L. *et al.* Clearance of persistent hepatitis C virus infection in humanized mice using a claudin-1-targeting monoclonal antibody. *Nat. Biotechnol.* doi:10.1038/nbt.3179