Moving closer to a mouse model for hepatitis C

Drugs to treat hepatitis C are expensive and not fully effective, and there is no vaccine. So there has been intense interest in developing mouse models of infection with hepatitis C virus (HCV), which only afflicts humans and chimpanzees.

Two studies[1,2] bring researchers closer to this goal by identifying a factor essential for HCV entry into liver cells, its primary target. Alexander Ploss *et al.*[1] and Shufeng Liu *et al.*[2] report that the virus binds occludin, a component of tight junctions. Expressing human occludin in mouse cells, along with another human protein previously identified as a viral target, enables the virus to enter and infect the cells. What do the findings mean for the quest to develop a mouse model for HCV, which infects 3 to 4 million people each year worldwide?

Stanley M. Lemon:

The identification of human occludin as an essential host partner in cell entry spotlights the central role of the tight junction in HCV infection and brings us one step closer to a mouse model of hepatitis C.

Many hurdles, however, remain, including identification of human proteins essential for subsequent steps in the viral life cycle, such as RNA synthesis and virion assembly. Also, although it will facilitate antiviral and vaccine development, a mouse model may have limited ability to unravel crucial issues in HCV pathogenesis, such as mechanisms underlying viral persistence.

HCV's extraordinary relationship to its human host is reflected in its ability to exploit human but not mouse occludin during cell entry. Similar key differences between the human proteins HCV targets for immune evasion and their mouse homologs are likely to limit the extent to which a mouse model can mimic human infection.

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Sergio Abrignani:

Currently available small animal models of HCV infection are based on transplant of human hepatocytes into immunodeficient mice[5]. Despite the usefulness of these models in testing antiviral drugs or assessing passive immunotherapy *in vivo*, they are laborious and unsuitable to study immune responses and develop vaccines.

The new findings are a big step toward the development of a practical and more 'physiological' mouse model of HCV infection. But viral entry is not the whole story. HCV RNA may require specific adaptive mutations to replicate efficiently in mouse cells, and little is known about the ability of mouse cells to foster assembly and release of infectious virus particles. The development of a mouse model of HCV infection is therefore likely to require additional efforts.

Chief Scientific Officer, National Institute of Molecular Genetics, Milan, Italy.

> "I, for one, am very excited about the possibilities.—Dennis R. Burton"

Dennis R. Burton:

The study of viruses and their interplay with the immune system is greatly helped by the availability of small animal models. I feel this acutely when I look at the beautiful work being done on the activity of antibodies against flaviviruses in straightforward mouse models—as we struggle with HIV in expensive monkeys, and HCV in a very difficult and complicated severe combined immunodeficient mouse system involving human liver grafts.

How much better it would be if one could humanize a mouse! Two groups have begun to attack this problem[1,2]. Ploss *et al.*[1] take a logical and elegant approach to the problem by screening the ability of a complementary DNA library from a highly permissive HCV cell line to render a nonpermissive cell line infectable with HCV. Do their findings mean transgenic mice can now be infected with HCV? Probably not, as it's likely that there are more problems ahead. But I, for one, am very excited about the possibilities.

Professor, Department of Immunology and Microbial Science, Scripps Research Institute, La Jolla, California, USA.

Ralf Bartenschlager:

The new studies provide key information on a host cell dependence factor of HCV infection. However, the way toward a fully permissive small animal model may still be long because HCV replication is inefficient in mouse cells[3,4] and assembly seems to be very much impaired (G. Koutsoudakis, V. Lohmann and R.B., unpublished data). The elucidation of additional host cell restriction and dependence factors governing the species specificity of HCV remains a challenging task, but the described species specificity of HCV receptors[1] provides an important starting point.

Professor, Department of Molecular Virology, University of Heidelberg, Germany.

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3. Uprichard, S.L., Chung, J., Chisari, F.V. & Wakita, T. Replication of a hepatitis C virus replicon clone in mouse cells. *Virol. J.* **3**, 89 (2006).
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