LIVER DISEASE

Quest to find new mouse models for liver diseases

Knowledge of the development and progression of liver diseases as well as the generation of efficient and effective therapeutics has been hampered by the lack of animal models of liver disease. Now, two papers published in Nature and the American Journal of Physiology—Gastrointestinal and Liver Physiology have used mouse models to advance the quest to understand and treat hepatitis C and NASH.

In the first paper, Charles M. Rice, Alexander Ploss and colleagues have generated a genetically humanized mouse, in which the entire life cycle of HCV infection can be modelled. This model could be used for preclinical testing of drug and vaccine candidates. Considering that current antiviral treatments for HCV—a leading cause of liver diseases, including fibrosis and cirrhosis—are poorly tolerated and ineffective in the majority of patients and that no vaccine is currently available, this model could have far-reaching therapeutic implications.

“HCV has a narrow host range, infecting naturally only humans and chimpanzees,” explains Ploss, corresponding author of this study. “Chimpanzees have been instrumental in the discovery of HCV and the characterization of the course of HCV infection. However, use of large apes for biomedical research is constrained by challenging logistics, high costs and ethical concerns, creating a pressing need for alternative model systems,” he adds.

Previous research from this group led to the identification of the minimal set of human factors (namely, CD81 and occludin) that render mouse cells susceptible to HCV infection, both in vitro and in vivo. However, the full HCV life cycle (including viral RNA replication and virion assembly and release) were not supported in this system. Now, the researchers have demonstrated that transgenic mice that stably express human CD81 and occludin support HCV entry, but innate and adaptive immune responses restrict HCV infection in vivo. Blunting of antiviral immunity in mice resulted in measurable virus in blood and liver after HCV infection. Moreover, direct-acting antivirals blocked the production of de novo infectious particles in these mice, providing evidence that the whole HCV life cycle was being completed.

“In this study we provide proof-of-concept that the entire HCV life cycle can be recapitulated in inbred mice, which is an important step forward, but the system is not perfect yet,” concludes Ploss. “It remains our goal to further improve our model to establish HCV infection in more immunocompetent hosts, which could then be used to study immunological mechanisms of chronicity and to prioritize vaccine candidates. We can also now apply mouse genetics to study liver disease progression in the context of HCV infection.”

In the second paper, Jason R. Clapper et al. have established a preclinical mouse model of NASH that could be used to assess liver pathology both before and after drug treatment. “Hallmarks of NASH, such as inflammation and fibrosis, are difficult to induce in a manner that recapitulates the disease aetiology and pathology observed in the clinic,” Clapper states.

“An overlooked feature in the application of preclinical models is the failure to determine the disease stage prior to pharmacological treatment; as is seen clinically, animals maintained on an experimental diet will develop NAFLD at differing rates and of varying severity,” Clapper explains. In this study, mice fed a ‘Western’ diet containing 40% fat, 22% fructose and 2% cholesterol progressed through three stages of NAFLD—steatosis, steatohepatitis with fibrosis and cirrhosis—as determined using both histological and biochemical methods. A key finding from this study is that mice developed NASH heterogeneously and at different rates, mirroring the situation in the clinic. Of note, the researchers established a liver biopsy method that enabled assessment of disease stage. Indeed, tissue samples obtained by biopsy were also sufficient for gene and protein expression analyses, and so liver pathology could be assessed objectively both before and after mice underwent treatment.

Clapper and co-authors believe that “the disease model we have developed, coupled with the biopsy technique, offer a powerful tool for researchers to not only test novel agents for anti-NASH activity, but to also identify markers of disease progression, which may translate to humans and to clinical practice”. An eventual goal of these researchers is to find objective markers that can be evaluated noninvasively.

Although it is still early days, the development of these mouse models provides opportunities to discover and screen new drugs and vaccine candidates for the treatment of multiple liver diseases. Hopefully, the findings from these mouse models can be translated into patients and into clinical practice. Let the quest continue!

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