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NEWS RELEASE
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Hepatitis therapy: Kupffer cells adjust the balance between pathogen control and hepatocyte regeneration

Hannover and Amsterdam, January 17, 2018 – Inflammation of the liver can result from different causes. Besides infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), other viruses such as cytomegalovirus (CMV) are able to trigger acute hepatitis. Sometimes hepatitis induces fever and flu-like symptoms, however, it may also damage the liver and might even result in acute liver failure. Yet, currently there is no general agreement on how acute hepatitis should be treated: Should the immune response against the viral pathogen be reinforced or inhibited? Scientists from TWINCORE have now published new insights on the processes involved in liver inflammation in the *Journal of Hepatology*: Type I interferons, on the one hand, limit viral replication and thereby help the immune cells to control the viral pathogen. On the other hand, type I interferons delay the regeneration of immune cells, which are important to adjust and maintain the immune balance within the liver during acute inflammation.

“So far, it has been assumed that viral replication itself destroys liver cells,” says Katharina Borst, scientist at the Institute for Experimental Infection Research, TWINCORE, Hannover, Germany. “Meanwhile we also know that local inflammatory processes can damage the liver.” This is critical knowledge, because, if the inflammatory reaction and not the virus accounts for liver damage, one should not enhance the inflammation within the already inflamed organ by treatment with an inflammatory cytokine such as type I interferon. “On the other hand, in clinical practice it is well established that type I interferon is an effective treatment during acute hepatitis and that it protects the liver,” argues Dr. Theresa Frenz, also scientist at the Institute for Experimental Infection Research, TWINCORE. At first glance this is a paradoxical situation that needs clarification.

Therefore, the scientists set out to understand the mechanism by which type I interferon works in the liver. To understand the local immune responses, they analyzed Kupffer cells, which are liver-resident scavenger cells within the immune system. The researchers used vaccinia virus to infect livers that either could or could not detect type I interferon, or in which only the Kupffer cells or the hepatocytes, the main cell type of the liver, could or could not detect type I interferon.

“This experiment showed us that hepatocytes do not need type I interferon to combat viral infection, since we could not find differences, regardless of whether we analyzed normal livers or livers in which

only hepatocytes did not detect type I interferon," says Katharina Borst. "This is surprising, since hepatocytes are the main target cell for type for infection."

However, type I interferon seems to be important for Kupffer cells, says Dr. Frenz: "We believe, that type I interferon triggers Kupffer cells to take up infected cells and undergo apoptosis (suicide) afterwards, since surprisingly, Kupffer cells disappear after infection." The body replaces those lost Kupffer cells by scavenger cells, which develop from the bone marrow. Such cells are not "real" Kupffer cells, but they still take over similar tasks. Interestingly, this process is accelerated if the bone marrow cells cannot sense type I interferon," says Ms. Borst. "Obviously, type I interferon is very important to adjust the regulation of inflammatory processes."

"We verified that therapeutic treatment of acute viral hepatitis with type I interferon is reasonable, since it activates local immune cells and helps to eliminate the virus," concludes institute director Prof. Ulrich Kalinke. "However, in order to better support the regeneration of the inflamed liver, we need to learn more about the balance of enhancement and modulation of inflammation. This will be the basis to develop new therapeutic interventions for acute hepatitis."

Notes for editors

The article is "Type I interferon receptor-signaling delays Kupffer cell replenishment during acute fulminant viral hepatitis," Katharina Borst, Theresa Frenz, Julia Spanier, Pia-Katharina Tegtmeyer, Chintan Chhatbar, Jennifer Skerra, Luca Ghita, Sukumar Namineni, Stefan Lienenklaus, Mario Köster, Mathias Heikenwaelder, Gerd Sutter, and Ulrich Kalinke (https://doi.org/10.1016/j.jhep.2017.11.029). It appears in the *Journal of Hepatology* published by Elsevier.

About the *Journal of Hepatology*

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About EASL

In the fifty plus years since EASL was founded, it has grown from a small organization that played host to 70 participants at its first meeting, to becoming the leading liver association in Europe. EASL attracts the foremost hepatology experts as members and has an impressive track record in promoting research in liver disease, supporting wider education, and promoting changes in European liver policy. www.easl.eu

About TWINCORE

TWINCORE, Centre for Experimental and Clinical Infection Research, Hannover, Germany, is a joint venture between the Hannover Medical School and the Helmholtz-Centre for Infection Research in Braunschweig. The scientists perform infection research to improve prevention, diagnosis, and treatment of human infectious diseases. Multidisciplinary research teams integrate clinical and basic researchers. Together, they strive to channel knowledge arising from basic research into clinical practice, and also to translate clinical observations into new insights into the mechanisms of disease. www.twincore.de/en

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