Website address:
https://www.gesundheitsindustrie-bw.de/en/article/news/the-critical-balance-between-liver-fibrosis-and-liver-regeneration

The critical balance between liver fibrosis and liver regeneration

When the liver has been damaged, a receptor protein of the hepatic stellate cells called endosialin controls the balance between liver repair and scar formation. A team of researchers from Heidelberg and Mannheim has shown that endosialin is a positive regulator of fibrogenesis and a negative regulator of hepatocyte proliferation. Endosialin therefore seems to be a promising therapeutic drug target in non-neoplastic settings.

Liver fibrosis is a reaction of the organ to persistent injuries or diseases that are caused, for example, by heavy drinking or drugs, chronic viral infections or genetic defects. Fibrosis is characterised by the formation of excess connective tissue at the expense of the liver parenchyma (hepatocytes), a wound-healing process that is reversible, at least in principle. However, chronic damage eventually leads to progressive, irreversible scarring and cirrhosis – with a high risk of developing liver cancer. Hepatic stellate cells (HSC) play a key role in the development of fibrous tissue (a process known as fibrogenesis). HSC are specialised connective tissue cells located in the perisinusoidal space (also called space of Disse) between the hepatocytes and the endothelial cells (squamous cells that line the interior surface of blood vessels, including the liver sinusoids). They store vitamin A and regulate blood flow; liver injuries trigger HSC, they proliferate and secrete collagen-1 molecules into the perisinusoidal space.

Endosialin plays a key role in liver fibrogenesis

A team of researchers from Heidelberg and Mannheim led by Prof. Hellmut Augustin has now demonstrated that a receptor called endosialin on the surface of stellate cells plays a key role in controlling the critical balance between fibrogenesis and liver regeneration. The scientists had previously shown that, in the liver, this receptor is exclusively found on HSC and portal fibroblasts rather than on the endothelial cells as was originally assumed. Endosialin belongs to the family of C-type lectin transmembrane receptors, which are calcium-dependent carbohydrate- and glycoprotein-binding proteins.

While only limited amounts of endosialin were detectable in HSC in healthy liver tissue of humans and mice, the scientists found that endosialin expression was considerably elevated in activated HSC in early stages of fibrogenesis. Expression of the protein was down-regulated once more in advanced stages of liver cirrhosis. In mice with liver damage induced by carbon tetrachloride (CCl_4), endosialin was produced by vitamin-A positive HSC primarily in the early, active phase of fibrosis; subsequently, more collagen-1a was formed.

Prof. Dr. Hellmut G. Augustin, head of the Division of Vascular Oncology and Metastasis at the German Cancer Research Center (DKFZ-ZMBH Alliance) in Heidelberg and the Department of Vascular Biology and Tumor Angiogenesis at the Centre for Biomedicine and Medical Technology (CBTM) at the Medical Faculty Mannheim.

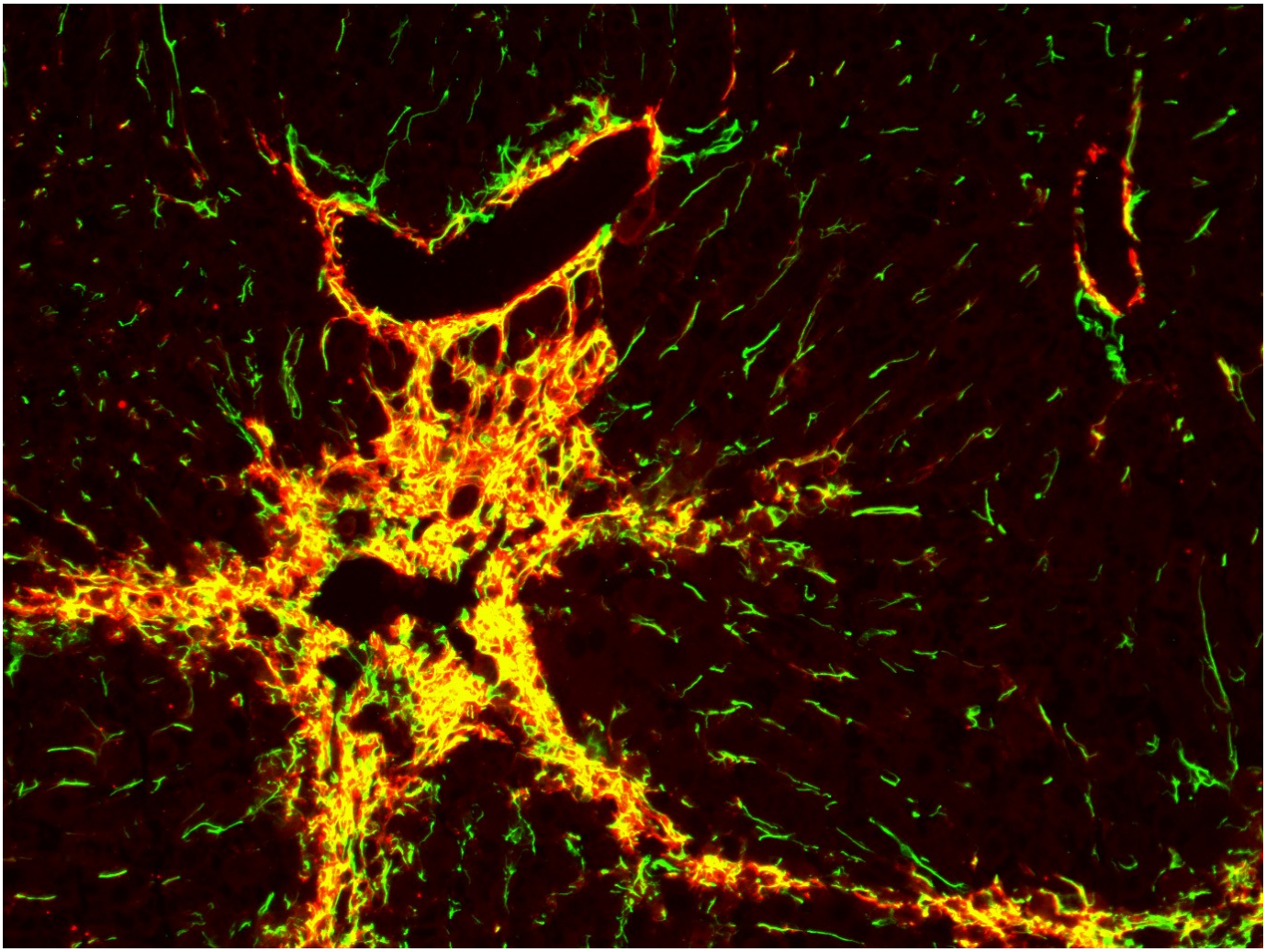
Dr. Carolin Mogler from the Division of Vascular Oncology and Metastasis at the DKFZ and the Institute of Pathology at the University of Heidelberg.

"Many molecules are produced at different levels after liver damage. But we were very surprised by the extent to which the stellate cells increase the production of endosialin," says Carolin Mogler, first author of the team's study that has recently been published in the renowned scientific journal EMBO Molecular Medicine. "These findings help us to better understand how liver fibrosis develops." In order to study the role of endosialin in fibrosis, the researchers used genetically modified mice that lacked the endosialin gene. Under normal (non-pathological) conditions, endosialin-deficient En(KO) mice did not visibly differ from wild-type (WT) mice.

However, chronic chemically induced liver damage (repeated administration of CCl_4) resulted in reduced fibrosis in En(KO) mice. Unexpectedly, acute-liver-damage-induced hepatocyte proliferation was considerably increased in endosialin-deficient mice.

Acute damage of the liver by partial hepatectomy (surgical removal of part of the organ) rather than by chemical poisoning induces regeneration processes and increases the proliferation (division rate) of hepatocytes. The researchers were also able to show here that the proliferation of parenchymal cells in EN(KO) mice exceeded that of WT mice. However, excessive liver growth was not observed and cell division rate kept its normal level. In their search for hepatocyte proliferation regulators that possibly reach increased levels in EN(KO) mice, the researchers discovered that insulin-like growth factor 2 (IGF2) was one such regulator.

Target molecule for the therapy of non-neoplastic liver diseases



Liver fibrosis of a mouse: the labelling of two characteristic proteins (yellow) shows the abnormal reorganisation of the organ.

Hellmut Augustin's team has identified through experiments that the lectin endosialin on the surface of hepatic stellate cells is a receptor that induces the formation of fibrous tissue and inhibits the growth of liver parenchyma. Endosialin is a positive regulator of fibrogenesis and a negative regulator of hepatocyte proliferation, and thereby controls the critical balance between the two processes, i.e. scar formation and liver regeneration. As the authors of the study point out, these characteristics make endosialin a promising target for drugs targeting liver fibrosis and similar non-neoplastic liver diseases.

Original publication:

Mogler C, Wieland M, König C, Hu J, Runge A, Korn C, Besemfelder E, Breitkopf-Heinlein K, Komljenovic D, Dooley S, Schirmacher P, Longerich T, Augustin HG: Hepatic stellate cell-expressed endosialin balances fibrogenesis and heaptocyte proliferation during liver damage. EMBO Mol Med 2015, DOI: 10.15252/emmm.201404246.

Article

16-Mar-2015
EJ
BioRN

The article is part of the following dossiers

Advances in the study and treatment of liver diseases