Liver cancer due to chronic inflammation: Tumour growth follows programmed cell death (apoptosis)

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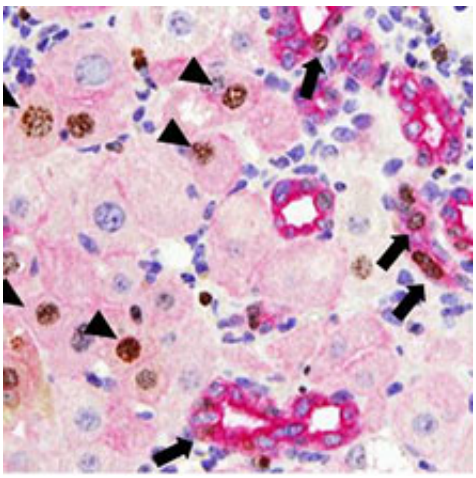

Immunohistochemical stainings of Ki67 and pancytokeratin (Ki67 is stained brown, pancytokeratin is stained pink) indicate proliferation of hepatocytes (arrowheads) and biliary epithelial cells (arrows) in TAK1/RIP3-deficient mice. Credit: Helmholtz Zentrum München

The death of numerous liver cells in the context of chronic inflammation due to apoptosis, a form of programmed cell death, can promote the formation of tumour cells in the liver. This insight significantly contributes to a better understanding of cellular processes in liver cancer development and thereby opens up new therapeutic approaches. A research team including scientists from the Helmholtz Zentrum München has reported this in the current issue of the scientific journal

Cell Reports.

Liver cancer (Hepatocellular Carcinoma, HCC) usually arises as the result of a chronic, inflammatory liver disease. The most common causes here are excessive alcohol consumption as well as a high-fat diet and also chronic infection with the hepatitis viruses B and C. In the course of the inflammatory process, the liver cells (hepatocytes) die more frequently due to programmed cell death. The result is increased cell growth, also referred to as compensatory proliferation, which can lead to tumour development.

A distinction is made between the two most important forms of self-induced cell death, namely apoptosis (programmed cell death) and necroptosis (programmed necrosis), which are based on different cellular mechanisms. Until now, it was not clear which form of cell death is decisive for the development of malignant liver tumours. The team working with Professor Dr. Tom Luedde from the RWTH Aachen University Hospital and Professor Dr. Mathias Heikenwälder from the Institute of Virology at the Helmholtz Zentrum München (HMGU) has now been able to verify that apoptosis precedes the development of abnormal liver cells. The scientists, including Florian Reisinger from the Institute of Virology (HMGU) and Dr. Kristian Unger from the Research Unit Radiation Cytogenetics (HMGU) showed this using mouse models. Moreover they discovered that in contrast, necroptosis prevents uninhibited cell proliferation and consequently the development of liver cancer.

These findings could form the basis for new approaches to therapy for liver cancer, which until now has been a form of cancer that cannot be adequately treated and that kills 800,000 patients around the world each year. "We now know which cellular signalling pathways are involved in liver tumour development", explains Heikenwälder. "In a further step we want to develop new treatment options, for example, by attempting to

pharmaceutically block the apoptosis itself or its signalling pathways. But any new therapy can also cause undesirable effects: In our experiments, we saw that blocking apoptosis under inflammatory conditions can result in bilirary obstruction (cholestasis) in the context of liver inflammation."

In upcoming investigations, the scientists want to verify their findings on the development of liver cancer and search for active substances that inhibit apoptosis while simultaneously causing the mildest possible side effects. The objective is to further develop the acquired knowledge in the sense of translational research in order to provide concrete benefits for society.

More information: Vucur, M. et al. (2013), RIP3 inhibits inflammatory hepatocarcinogenesis but promotes cholestasis by controlling Caspase-8- and JNK-dependent compensatory cell proliferation, *Cell Reports*. DOI: 10.1016/j.celrep.2013.07.035

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