Medical Xpress

A novel molecular link between cholesterol, inflammation and liver cancer

March 29 2017

Hepatocellular carcinoma (HCC) is a deadly disease with no effective cure that develops in the context of liver diseases associated with chronic inflammation. A recent research article published in *The Journal of Experimental Medicine* describes how important a protein called c-Fos is for HCC development, because it affects cholesterol homeostasis in hepatocytes, the main cells of the liver. Using genetically modified mouse models (GEMMs), Erwin Wagner, director of the Cancer Cell Biology Programme at the Spanish National Cancer Research Centre (CNIO), and his Genes, Development and Disease (GDD) team experimentally document how c-Fos modulates premalignant hepatocyte transformation and how this is linked to cholesterol and inflammation. Maintaining healthy cholesterol levels in the organism is therefore important for preventing liver cancer.

"The critical step to identify biomarkers and develop effective preventive therapies is a better understanding of the mechanisms responsible for cancer initiation", the authors state. For that, the scientists generated new mouse models that allowed them to investigate the very early steps of HCC development in the liver, something that is not feasible with patient samples.

Using these models, the authors were able to dissect the role of c-Fos, a component of a protein complex called AP-1 they had already connected to liver diseases (1-3). Erwin Wagner´s team switched on the expression of c-Fos in hepatocytes and monitored liver and whole body physiology in mutant mice. The scientists observed cell damage that progressed over

time, and measured a variety of markers for liver dysfunction and premalignant transformation of hepatocytes. Importantly, these alterations disappeared after switching off c-Fos expression.

All these changes, the authors say are due to decreased activity of a nuclear receptor crucial for cholesterol homeostasis. c-Fos induces hepatic accumulation of cholesterol and toxic cholesterol derivatives that damage hepatocytes and increase cancer risk.

Further experiments showed that removing c-Fos expression in the liver of GEMMs protects them from HCC, when exposed to chemical carcinogens. On the other hand, increasing c-Fos expression accelerates carcinogenesis. "This indicates -state the researchers- that c-Fos not only promotes but is also necessary for liver carcinogenesis and can be a useful therapeutic target to explore".

Wagner and colleagues decided to treat mice with the most commonly used cholesterol lowering drug. "We treated our mutant mice with statins and premalignant hepatocyte transformation was prevented", explains Latifa Bakiri from the GDD team and co-first author of the paper. These results suggest that statins may also prevent deleterious changes in hepatocytes caused by hypercholesterolemia and thus reduce inflammation and liver cancer. Most importantly, the study highlights the importance of maintaining a correct cholesterol balance through a healthy life style to prevent not only cardiovascular diseases, but also liver cancer.

More information: Liver carcinogenesis by FOS-dependent inflammation and cholesterol dysregulation. Latifa Bakiri, Rainer Hamacher, Osvaldo Graña, Ana Guío-Carrión, Ramón Campos-Olivas, Lola Martinez, Hans P. Dienes, Martin K. Thomsen, Sebastian C. Hasenfuss, and Erwin F. Wagner. (The *Journal of Experimental Medicine* 2017) DOI: 10.1084/jem.20160935

Provided by Centro Nacional de Investigaciones Oncológicas (CNIO)