A novel oncogenic network specific to liver cancer initiation

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Researchers headed by Erwin Wagner, the Director of the BBVA Foundation-CNIO Cancer Cell Biology Programme at the Spanish National Cancer Research Centre (CNIO), have deciphered how a stress-inducible gene regulator, AP-1, controls the survival of liver tumor-initiating cells. These results, published in the online edition of *Nature Cell Biology*, could provide new preventive strategies and identify potentially targetable molecules to prevent liver cancer.

Hepatocellular carcinoma (HCC) causes more than 500,000 deaths per year worldwide. While patients with chronic hepatitis virus B and C infections or liver cirrhosis are high-risk populations for HCC, measures aiming at preventing HCC development in these patients are limited. In addition, the long-term prognosis after surgical resection of HCC remains poor, due to the high rate of de novo recurrence and the lack of effective preventive therapy.

The critical step for developing effective preventive therapies, but also diagnostic markers and preventive strategies is to identify targetable molecules and pathways responsible for cancer initiation.

Using genetic mouse models specific for liver cancer initiation, researchers have discovered how the stress-inducible AP-1 gene regulator modulates liver tumor cell death in early stages of liver cancer. Mechanistically, AP-1 controls the expression of the epigenetic modulator SIRT6. Subsequently, SIRT6 represses Survivin, which is involved in programmed cell death.

Importantly, altering these proteins in mice even transiently during the initiation stage markedly impaired liver cancer development in mice.

The relevance of these findings was tested in more than 150 human tissue samples collected in patients from Asia and Europe. A clear correlation between these proteins and liver cancer initiation, but not in advanced HCCs, was observed.

These results connect liver cancer initiation with epigenetics and cell death, and give new insights into why patients with metabolic diseases where SIRT6 is important, are at risk of developing of liver cancer.

"Our study provides not only novel implications for the development of preventive therapies for high risk cirrhotic or post-resection patients, but also a new paradigm how one can molecularly dissect cancer initiation using mouse models in combination with the appropriate human samples", states Latifa Bakiri, author of the study.

The study was initiated in Erwin Wagner´s group at the IMP in Vienna and subsequently carried out at the Spanish National Cancer Research Centre (CNIO) and at the State Key Laboratory of Cell Biology, in Shanghai China led by Lijian Hui.

The study also involves the participation of clinical researchers at Fudan University in Shanghai and the Medical University of Graz, Austria.

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