REPORT
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CANCER

CONTRIBUTION OF THE MITOCHONDRIAL METABOLISM OF OXYSTEROLS AND BILE ACIDS TO LIVER CARCINOGENESIS

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The Project titled Contribution of mitochondrial oxysterol and bile acid metabolism to liver carcinogenesis, financed by La Marató de TV3 in its 27th edition dedicated to cancer, was accomplished thanks to the cooperation of two research teams located at the Institute of Biomedical Research in Barcelona (IIBB), belonging to the Spanish National Research Council (CSIC), and the University of Salamanca (USAL).

1. Overview

Hepatocellular carcinoma (HCC), the end-stage of chronic liver disease caused by different etiologic causes including virus, alcohol, and diet-induced fatty liver disease, is the most common cause of liver cancer and the second leading cause of cancer mortality worldwide, and the molecular mechanisms underlying it are still poorly understood. Hence it represents an important health burden to the public health systems due to its expected increase worldwide caused by its association with the pandemic outburst of obesity, type II diabetes and insulin resistance. It has been estimated that obesity represents an important risk factor for the development of HCC, which justifies the urgent need to find novel and more effective therapeutic treatments. The current available chemotherapy for HCC is limited and poorly effective, with the development of ill-defined mechanisms contributing to chemotherapy resistance. Although cholesterol is a key component of cell membranes, it has emerged as a key player in chronic liver disease transcending its classical role in cardiovascular and coronary health disease. Cells' need for cholesterol is met by its de novo synthesis or its supply from the diet and it is then distributed to different membrane bilayers where it is thought to determine membrane physical properties. Cholesterol is the substrate of key cell components, including vitamin D and steroid hormones in specialized tissues or bile acids in the liver. The latter process plays an important physiological role in the digestive tract and is self-regulated by a feedback inhibition involving intestine-liver communication to limit continued bile acid synthesis in hepatocytes from cholesterol. The trafficking of cholesterol to mitochondria in the liver represents an additional, alternative way to synthesize bile acids by a specialized pathway that escapes the regulatory control of feedback inhibition of the classical pathway. Although previous findings indicated that mitochondrial cholesterol determines mitochondrial function and chemotherapy resistance, the contribution of mitochondrial cholesterol metabolism to bile acids and oxysterols by a specialized pathway to HCC development has not been

previously determined. This is important, as this particular process, may represent a deregulated step in continued generation of bile acid/oxysterol metabolites that can impact not only mitochondrial function but also induce signaling pathways involved in cell proliferation and repair that ultimately contribute to HCC progression. The present project was designed to test this hypothesis using novel experimental genetic models and samples from patients with HCC.

2. Results

Our results have identified a new player, namely StARD1, a mitochondrial cholesterol transporter, whose induction in experimental models of liver tumor generation and samples from subjects with hepatocellular carcinoma correlates with an increase in more hydrophobic bile acids, suggesting that StARD1 may be a new therapeutic target for HCC. Furthermore, the development of this project has provided valuable information on the metabolic pathway of bile acid synthesis by hepatocytes, and more specifically on the stage of shortening the side chain of cholesterol in peroxisomes.

3. Relevance

The results derived from this project have a great relevance at the clinical, social and economic level since it has revealed a new model of experimentation, i.e. a mouse model with humanized liver, whose discoveries can be translated into practice more quickly and efficiently, which directly benefits human health. In addition, it points to StARD1 as a determining factor in the development and progress of HCC, making it a possible therapeutic target for which it is necessary to find specific inhibitors that should be taken and tested in clinical phases. Our findings open the doors to new research, bring new mechanisms, point out new biomarkers in the disease and propose new therapeutic targets that hopefully serve not only to improve the health status of people suffering from HCC but also to slow the progression of the disease.

4. Bibliographic data generated

1. Research articles (directly related to the project)

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