Universidad de Navarra
Facultad de Ciencias

MASTER'S DEGREE IN BIOMEDICAL RESEARCH
Research Project Proposal
Academic year 2023-2024

Project Nº 17

Title: High risk of liver cancer in acute hepatic porphyrias: Is the porphobilinogen deaminase a new metabolic tumor suppressor gene in hepatocellular carcinoma?

Department/ Laboratory Solid Tumors program. Hepatology Laboratory

Director 1 Antonio Fontanellas Romá
Contact: afontanellas@unav.es

Summary

Hydroxymethylbilane synthase (HMBS), also known as porphobilinogen deaminase (PBGD), catalyzes the third reaction in the heme synthesis pathway which takes place in all cells but predominantly in bone marrow erythroblasts and hepatocytes. Inactivating mutations in different genes along this pathway define a group of diseases known as porphyrias. Haploinsufficiency affecting HMBS is responsible for acute intermittent porphyria (AIP), the most prevalent and severe of the acute hepatic porphyrias. The development of liver cancer, mostly hepatocellular carcinoma (HCC), is recognized as a long-term complication of AIP since the 1980s. A recent study supports the notion that HMBS is a bona fide tumor suppressor gene in HCC. Thus, carriers of a HMBS germline mutation would be at an increased risk of bi-allelic HMBS inactivation by developing a second somatic mutation, which would foster malignant transformation. Given that the prevalence of likely-pathogenic HMBS mutations in the Caucasian population is 1:1,700 the involvement of HMBS deficiency in HCC development in non-cirrhotic livers may be underreported in asymptomatic carriers. The aim of this work is to characterize the appearance of HCC in AIP mouse models that carry one or two mutated HMBS alleles. To stimulate tumor formation, mice will be injected by a hydrodynamic procedure with plasmids expressing a mutated form of β-catenin, Myc or Telomerase reverse transcriptase (TERT). We will study which of these mutant protein favours tumor formation in porphyria model. Early tumor formation and survival in animals with one or two mutations in the HMBS gene will be studied compared with wildtype animals. A histological, biochemical and gene expression characterization in the tumor and in the peritumoral region will also be performed.

yes	X
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?