Research Project Proposal
Academic year 2019-2020

Project Nº 26

Title: Role of post-transcriptional modifications (PTMs) in the etiopathogenesis of cholangiocarcinoma: new diagnostic, prognostic and therapeutic strategy

Department/ Laboratory
Liver Diseases Group,
Department of Hepatology and Gastroenterology
Biodonostia Health Research Institute (Donostia University Hospital)
Paseo del Dr. Begiristain s/n
20014 Donostia - San Sebastian

Director: Dr. Jesus Maria Bañales
Contact: jesus.banales@biodonostia.org
Tel: +34 627401179 (Mobile) / +34 943006067 (Office)

Co-director: Dr. Pedro Miguel Rodrigues
Contact: pedro.rodrigues@biodonostia.org
Tel: +34 600611928 (Mobile) / +34 943006125 (Office)

Summary
Cholangiocarcinoma (CCA) includes a heterogeneous group of biliary malignant tumors characterized by dismal prognosis. Incidence is increasing worldwide, becoming a significant health problem. The etiopathogenesis of CCA remains largely unknown. Therefore, there is an urgent need to unveil the mechanisms involved in its development and progression in order to find new therapeutic targets and early diagnostic/prognostic biomarkers. Post-transcriptional modifications (PTMs) provide a rapid mechanism for the activation or inhibition of signaling pathways and metabolism. Among the different PTMs, NEDDylation and SUMOylation have been recently described and seem to regulate a wide range of cellular processes that are considered relevant for cancer. However, the role of NEDDylation and SUMOylation in CCA remains to be elucidated. Our preliminary data indicate that NAE1 (key enzyme in the NEDDylation pathway), and UBC9 (key enzyme in SUMOylation) expressions are markedly increased in CCA human cells lines, as well as in tumor tissue of patients (n=104), compared to normal conditions. Importantly, NAE1 and UBC9 expression correlated with tumor differentiation in CCA patients. Here, we hypothesize that NEDDylation and SUMOylation pathways may have a prominent role in cholangiocarcinogenesis, being potential biomarkers and therapeutic targets.
Aims:
1. Analysis of NAE1 and UBC9 expression in CCA and normal human liver tissue and correlation with clinicopathological features.
2. Determination of the role of NAE1 and UBC9 in the pathogenesis of CCA *in vitro* and *in vivo*.
3. Investigation of the role of NAE1 and UBC9 in normal human cholangiocyte biology.

Methodology:
1. CCA and normal liver samples from 3 large international cohorts.
2. Cell culture of CCA cells and normal human cholangiocytes.
3. Orthotropic tumor xenografts (mice).
4. CRISPR/Cas9 technology and siRNAs silencing NAE1 and UBC9.
5. Proliferation, cell cycle and cell death assays.
6. Expression analysis (qPCR, WB, IHC).

yes	**X**	**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**
no		