Research Project Proposal
Academic year 2018-2019

Project Nº 7

Title: Role of the transcription factor KLF15 in the etiopathogenesis of cholangiocarcinoma: new diagnostic, prognostic and therapeutic strategy

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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. Krüppel-like factors (KLFs) are a family of transcription factors that regulate different cellular processes and their expression and/or activities are altered in different diseases, including cancer. However, the role of KLFs in CCA remains totally unknown. Our preliminary data indicate that KLF15 expression is markedly decreased in CCA human cells lines, as well as in tumor tissue of patients (n=104), compared to normal conditions. Importantly, KLF15 expression correlated with tumor differentiation and with progression-free survival in CCA patients. Here, we hypothesize that KLF15 may have a prominent role in cholangiocarcinogenesis, being a potential biomarker and therapeutic target.

Aims:

1. Analysis of KLF15 expression in CCA and normal human liver tissue and correlation with clinicopathological features.
2. Determination of the role of KLF15 in the pathogenesis of CCA *in vitro* and *in vivo*.
3. Investigation of the role of KLF15 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 lentiviruses overexpressing KLF15.
5. Proliferation, cell cycle and cell death assays.
6. Expression analysis (qPCR, WB, IHC).

yes	**X**
no	

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