Marató TV3 2018 (CANCER): Epigenetic Characterization of Cholangiocarcinomas

Description

Cholangiocarcinoma (CCA) is a rare type of cancer and the second most common hepatobiliary malignancy, accounting for 10 to 20% of primary liver cancers. In the recent years, different groups have published data on the molecular biology of CCA, describing a complex pathogenesis, involving various molecular pathways, some of them potential therapeutic targets, such as mutations in IDH1, IDH2, BRAF, PI3K, MET, or translocations in FGFR2. Among them, IDH1/2 mutation represents 20% of patients with CCA. This IDH-mutant generates an oncolometabolite, D-(R)-2HG (D2HG), responsible for many, if not all, biological effects of cancer-associated IDH mutations. D2HG competitively inhibits a large family of að-KG-dependent enzymes (TET, JmJC) which results in a global increase of DNA and histone methylation. A comprehensive understanding of how IDH1 mutation alters chromatin states is lacking in CCA and needs to be stablished. Here we will analyse the epigenome of CCA_PDXs and cholangiocarcinoma cell lines in terms of histone methylation patterns, DNA accessibility, DNA methylation and transcriptome profiling of both protein coding and lncRNAs in IDH1 wildtype and mutant population. Therefore, we propose to combine the latest high-throughput epigenome and transcriptome profiling techniques together with cutting-edge computational analyses to analyse a unique set of CCA patient derived models.

The goal of this project is to perform an integrative analysis to characterize CCA molecularly and epigenetically and shed light on the relation between the genetic and epigenetic architecture of the disease. We also plan to test different inhibitors in IDH1 CCA_PDXs models and to study the biology behind this activity to identify potential biomarkers.

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