IDENTIFICATION OF EPIGENETIC VULNERABILITIES IN THE ADENOMA-CARCINOMA SEQUENCE

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Introduction: Numerous studies have documented the functional effect of different driver mutations on the development and progression of colorectal cancer (CRC). However, the molecular-level impact of each of these mutations on the epigenome/transcriptome, as well as the phenotype-related longitudinal effects of these mutations have not been characterized in detail. This work proposes an experimental design based on the integration of different -omic layers in order to identify molecular vulnerabilities with therapeutic potential in the adenoma-carcinoma sequence.

Methods: The proposed experimental model contemplates the introduction of sequential mutations in the APC/KRAS/TP53 and SMAD4 genes with CRISPR/Cas9 technology in human colon organoids obtained from healthy mucosa. To determine the molecular alterations at each step of the sequence, a paired RNA expression and DNA methylation analysis will be performed at the whole genoma level with the respective massive next-generation sequencing technologies / EPIC arrays. Finally, to identify possible functional associations between the epigenome/transcriptome, an integration analysis of these -omics will be performed with novel computational algorithms, also including the integration of these data with information available from international consortia.

Results: The project is currently in the initial stages of development. The model and the most updated results available to date will be discussed in detail during the congress.

Conclusions: These results will allow the identification of molecular vulnerabilities with therapeutic potential in the context of CRC.