OVERVIEW

We focus on the molecular pathophysiology of pancreatic ductal adenocarcinoma (PDAC) and urothelial carcinoma (UC), adopting a disease-oriented approach. We use cultured cells, genetically modified mice, and patient samples, giving similar weight to the 3 model systems. Primary observations are made at either of these levels and are then extended through additional work. To translate the findings, we bring this knowledge to a ‘population’ level, harnessing information and samples from large patient cohorts.

In PDAC, we study cell differentiation as a potent tumour suppressor mechanism acting early during carcinogenesis. We use the excellent genetic mouse models available because these processes cannot be readily studied using human samples. PDAC can originate both in pancreatic progenitors and in acinar cells. Understanding the contribution of these cell types to PDAC is crucial to design better strategies for early tumour detection and prevention in subjects at risk.

“In UC, we focus on identifying new genes, using them for improved tumour taxonomy, characterising their mechanisms of action, and applying this knowledge for improved prediction of outcome and therapy.”
PANCREAS CANCER MOLECULAR PATHOPHYSIOLOGY

We are analysing the tumour suppressor role of several transcription factors involved in pancreatic differentiation. PI3MC is characterised by highly prevalent alterations in KRAS, p16, TP53, and SMAD4, and by low-frequency alterations in a plethora of other genes converging in a few critical genetic pathways. The currently accepted progression model proposes that the sequential acquisition of these genetic changes drives the development of PanIN-1, -2, and -3 lesions. We are previously highlighting the weaknesses of this model. Using mutant KRAS as the driving oncogene in a pancreatic Gata4-null background, we have shown that PDAC can be initiated from pancreatic progenitors or adult acinar cells without the development of acinar-ductal metaplasia (ADM) or preneoplastic PanINs (FIGURE 1). These findings, together with recent evidence using whole genome sequencing of human PDAC, suggest the presence of a plethora of other genes converging in a few critical genetic pathways involved in pancreatic differentiation. We are analysing the tumour suppressive role of several transcription factors involved in pancreatic differentiation. Importantly, Nfia2 controls both epithelial differentiation and inflammatory programmes, providing mechanistic evidence that these processes are linked at the transcriptional level in pancreatic cells. We are also exploring the potential of enhancing Nfia2 activity to suppress pancreatitis and tumour development. This work benefits from a close collaboration with the CNIO Groups of E. Wagner and N. Malats.

UROTHELIAL CARCINOMA (UC) GENETICS, BIOLOGY, AND CLINICAL TRANSLATION

Our goal is to refine current knowledge on the genomic landscape of UC and apply this in the clinical setting. Through exome sequencing we identified STAG2 and RBM10 as new UC genes that are more broadly involved in human cancer. STAG2 codes for a cohesin subunit; its inactivation in UC is not associated with aneuploidy, suggesting that regulation of chromatin architecture and gene expression mediate its tumour suppressor function. Transcriptomic analyses of human tumours and cultured cells, as well as biochemical studies, support a cooperation with transcriptional networks involved in urothelial differentiation. In collaboration with A. Losada (CNIO), we have developed a conditional Stag2 knockout strain and are analysing the role of cohesin in urothelial cell transformation. RBM10 codes for a splicing factor and it is mutated in several other epithelial tumours. Inactivation in UC is not associated with stage or grade, but it occurs mainly in tumours with urothelial differentiation. In collaboration with J. Valcárcel (CRG, Barcelona), we have generated a conditional Rbmi10 knockout strain and are analysing the molecular mechanisms through which this gene contributes to UC development using a combination of molecular and bioinformatics strategies. These studies will be complemented with the use of normal urothelial organoids, for which we have established robust culture methods and have shown their strict dependence on EGF and Wnt signalling. We have characterised an organoid cell-of-origin with stem cell properties in vitro and have identified conditions promoting urothelial differentiation (FIGURE 2). In addition, we are expanding these studies to human bladder cancers.

Within the context of a project funded by the Spanish Association Against Cancer (ARCC), we are analysing the clinical usefulness of the new UC taxonomy. The main aim is to identify predictors of outcome and response to cisplatin-based therapies in patients receiving perioperative chemotherapy. These studies are linked to the design of clinical trials that include molecular stratification criteria. This work is carried out in collaboration with N. Malats at the CNIO and the SOGUG cooperative group.