We focus on the molecular pathophysiology of pancreatic ductal adenocarcinoma (PDAC) and bladder carcinoma taking a disease-oriented approach. These tumours present very distinct clinical challenges. We learn from patient samples, cultured cells/organoids, and genetically modified mice. To translate the findings, we bring this knowledge to a “population” level — leveraging on information and samples from large patient cohorts — together with Núria Malats (CNIO).

PDAC has a dismal prognosis even when diagnosed early. We aim at dissecting the molecular mechanisms involved in very early steps of tumour development, harnessing the power of mouse genetic editing. A main hypothesis is that cell differentiation is an early and potent tumour suppressor mechanism. Understanding the contribution of early molecular events is crucial to design better strategies for prevention and early tumour detection.

Bladder cancer presents with a very wide clinical and pathological heterogeneity. We aim at acquiring knowledge about the underlying biology that might be leveraged towards improved tumour subclassification, prediction of outcome, and therapy.

“A new mouse strain carrying an exon 6 deletion in Ctrb1 recapitulates the human variant associated with PDAC. A mutant, insoluble, CTRB1 truncated protein is present in the pancreas of these mice, associated with a dramatic ER stress phenotype.”
United States (USA). Results and Discussion: Despite the significant progress in understanding the molecular mechanisms driving PDAC, many questions remain unanswered. One of these questions pertains to the role of genetic variants in PDAC development.

First, we have extensively studied the role of NR5A2 using a knockdown model in the tumor suppressor mechanism. Among the few GWAS studies required for full acinar differentiation, a few other GWAS hits associate genes with roles in cancer function, such as CTRB1, XRBP1, and CTRB2. These observations have strengthened the notion, pioneered by our lab, that cell differentiation is the first tumour suppressor mechanism in the pancreas. Among the processes participating therein are inflammation and ER stress response. We have extensively studied the role of NR5A2 using heterozygous mice. Recently, we focussed on a risk variant in CTRB2 that has been finely mapped as a deletion in exon 6. We generated, with Sagrario Ortega (CNIO), a new mouse strain carrying the corresponding exon 6 deletion in CTRB2, the mouse orthologue of the human gene. CTRB1 mice are viable and display normal growth until adulthood. The mutant CTRB1 protein has a smaller molecular mass and is largely present in the insoluble fraction of pancreatic lysates, unlike the wild-type protein. While the pancreas of 5-month-old heterozygous mutant mice shows a normal histological appearance, ultrastructural analysis shows dramatic alterations of the endoplasmic reticulum, with extensive cisternal dilation, abundant cytoplasmic aggregates, partial loss of zymogen granules, and even some nuclear inclusions.

Surprisingly, some acinar cells appear spared despite the germline nature of the mutation introduced. Similar, but less dramatic, changes occurred in heterozygous mice. RNA-Seq analysis of the pancreas of Ctrb1 heterozygous mice revealed a down-regulation of the acinar programme and an up-regulation of ER stress changes occurred in heterozygous mice. RNA-Seq analysis of the pancreas of 3-month-old mice revealed a down-regulation of representative pathways. We interpret these findings as an adaptation of the acinar programme and an up-regulation of ER stress pathway activity. We interpret these findings as an adaptation of the acinar programme and an up-regulation of ER stress pathway activity. We interpret these findings as an adaptation of the acinar programme and an up-regulation of ER stress pathway activity.

Furthermore, we continue to collaborate with our clinical colleagues in the conduct of clinical studies with a strong translational component. We have generated, with Sagrario Ortega (CNIO), a new mouse strain carrying the corresponding exon 6 deletion in CTRB2, the mouse orthologue of the human gene. CTRB1 mice are viable and display normal growth until adulthood. The mutant CTRB1 protein has a smaller molecular mass and is largely present in the insoluble fraction of pancreatic lysates, unlike the wild-type protein. While the pancreas of 5-month-old heterozygous mutant mice shows a normal histological appearance, ultrastructural analysis shows dramatic alterations of the endoplasmic reticulum, with extensive cisternal dilation, abundant cytoplasmic aggregates, partial loss of zymogen granules, and even some nuclear inclusions.

Pancreatic cancer molecular pathophysiology

Genome-wide association studies (GWAS) have identified common genetic variants associated with PDAC risk. Several of them are associated with genes involved in acinar cell biology, including NR5A2 and HNF1A coding for transcription factors required for full acinar differentiation. A few other GWAS hits associate genes with roles in cancer function, such as CTRB1, XRBP1, and CTRB2. These observations have strengthened the notion, pioneered by our lab, that cell differentiation is the first tumour suppressor mechanism in the pancreas. Among the processes participating therein are inflammation and ER stress response. We have extensively studied the role of NR5A2 using heterozygous mice. Recently, we focussed on a risk variant in CTRB2 that has been finely mapped as a deletion in exon 6.

Urothelial bladder cancer genomics, biology, and clinical translation

We focus on understanding 2 new tumour suppressor genes that are mutated in bladder cancer that we identified through exome sequencing: STAG2 and RBM10. STAG2 codes for a cohesin subunit and RBM10 codes for a splice-splifying regulator. We have generated conditional mouse models for these 2 genes and are exploring their role in development and urothelial biology as well as their cooperation with other cancer genes.

Bladder cancers that do not invade muscle largely maintain a luminal/urothelial phenotype characterised by the expression of transcription factors involved in the activation of this programme, such as GATA3 and FOXA1. However, upon invade muscle, a fraction of tumours loses this identity and displays a basal/squamous phenotype that is reminiscent of that of basal cells in the urothelium. This is generally associated with the loss of normal translational-type factors. To acquire a more detailed understanding of the molecular mechanisms involved in this process, which is associated with more aggressive tumours, we set out to systematically identify novel transcriptional regulators that might participate in this process. Using bulk and single cell transcriptomic data from bladder cancer organoids and tumours classified as luminal or basal/squamous, we identified differentially expressed factors and searched for the enrichment of their binding motifs in accessible regions of chromatin and for experimental evidence in support of their binding. In addition, we considered their tumour specificity by selecting available information from tumours and normal urothelium. This integrative work has unveiled several new transcription factors that are candidates to participate in urothelial transformation, including FOXG1, MXC/MOM, TRIMs, API proteins, and TFAP2, among others.

In addition, we continue to collaborate with our clinical colleagues in the conduct of clinical studies with a strong translational component.