We focus on the molecular pathophysiology of pancreatic ductal adenocarcinoma (PDAC) and urothelial bladder carcinoma (UBC) using 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 to dissect the molecular mechanisms involved in very early steps of tumour development, harnessing the excellent genetic mouse models available. 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.

UBC presents with very wide clinical and pathological heterogeneity. Our aim is to acquire knowledge about the underlying molecular pathways and to apply it for improved prediction of outcome and therapy.

“We have shown that, in vitro, STAG2 is involved in the control of urothelial cell differentiation, in agreement with the fact that STAG2 mutations are associated with luminal-type bladder cancer.”
Pancreatic cancer molecular pathophysiology

The genetic/genomic changes associated with PDAC have been extensively described by genome consortia, and there is increasing interest in defining the molecular changes that precede tumour development. Our laboratory has pioneered the notion that cell differentiation is the first tumour suppressor mechanism in the pancreas. Focusing on acinar cells, we have identified several novel transcriptional factors (TFs) involved - including GATA6, GATA4, NR5A2, HNF1A, and NFIC. Dysregulation of these transcriptional programmes is associated with a scenario of pre-inflammation or inflammation, providing the basis for the pharmacological and genetic manipulation of acinar differentiation as a tumour preventative strategy. We have generated super-Nr5a2 mice where the concept that inducible differentiation has a tumour protective role is currently being tested (with Sagrario Ortega, CNIO).

GATA6 and GATA4 are critically involved in the maintenance of the "classical" phenotype in PDAC but their distinctive roles in normal acinar cells are not well established. Gata4 deletion in pancreatic progenitors results in a histologically adult normal pancreas with reduced expression of digestive enzyme transcripts, in sharp contrast with the requirement of Gata6 for acinar cell maintenance in adult mice. We and others have shown that activation of mutanacins in the pancreas leads to increased activity of inflammatory and cell cycle pathways. Deletion of Gata6 or Gata6b has opposite effects on the activation of inflammatory pathways in this context, but both genes act as tumour suppressors, indicating the existence of shared and unique roles for them in pancreatic homeostasis and carcinogenesis (FIGURE 1A-C).

To better understand how these TFs cooperate in normal pancreas and in early steps of tumorigenesis, we have built a gene regulatory network integrating public ATAC-Seq data and pancreas and in early steps of tumorigenesis, we have built a gene regulatory network integrating public ATAC-Seq data and pancreatic enhancers. This network reveals dramatic changes in TF hierarchies upon perturbation through induction of pancreatitis, KRAS activation, TF deletion, or a combination thereof. Our overarching goal is to establish the rules governing the control of acinar differentiation and their contribution to preneoplasia and cancer.

Urothelial bladder carcinoma (UBC) genetics, biology, and clinical translation

We focus on understanding two new UBC tumour suppressor genes that we identified through exome sequencing: STAG2 and BRMTO. STAG2 codes for a cohesin subunit and BRMTO codes for a splicing regulator. We have generated conditional mouse models for these two genes and are exploring their role in development and in urothelial biology, as well as their cooperation with other cancer genes.

Increasing evidence shows that STAG2 acts as a tumour suppressor through rather unique mechanisms, largely unrelated to the canonical role of cohesin in chromosome segregation. STAG2 alterations occur early during tumorigenesis. Therefore, we are using both normal urothelial cells and tumour cell lines to identify the impact of STAG2 at the genomic and cellular levels. Using RT112 cells, we have integrated ChIP-seq, HiChromatin interaction data, and RNA-Seq to assess the impact of STAG2 knockdown. The STAG2 complex mediates short- and mid-range interactions that engage genes at higher frequency than cohesin-STAG1. STAG2 knockdown results in the down-regulation of luminal differentiation programmes and up-regulation of basal programmes. These findings are at odds with the fact that STAG2 mutations are associated with luminal-type bladder cancers, suggesting an intermediate luminal differentiation phenotype. STAG2 knockdown does not affect compartment and domain boundaries, but it rewires intra-TAD RNA interactions and leads to the de-expression of lineage specifying genes (FIGURE 2) (in collaboration with M. Marti-Renom, CRG, Barcelona).

Our translational studies expand several clinical trials with a strong translational component carried out in collaboration with Nuria Malats and Spanish uro-oncologists.

**PUBLICATIONS**