Gaining Insights into Tumor Cell Plasticity of Colorectal Cancer using Multi-omics Profiling

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MOTIVATION

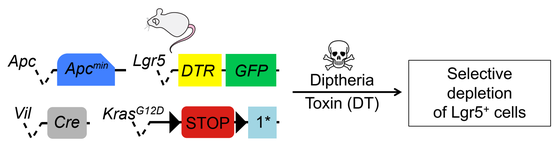
- Colorectal cancer (CRC) is a clinically diverse disease and a leading cause of cancer-related deaths
- Cancer stem cells (CSCs) play a key role in tumor maintenance and are thought to resist to therapy and cause relapse, therefore targeting CSCs may improve survival
- CSCs ablation through administration of diphtheria toxin (DT) has different impact on tumor growth: continuous growth in colon tumors versus tumor regression in liver metastases
- Discontinuation of DT treatment leads to re-initiation of tumor growth

Questions:

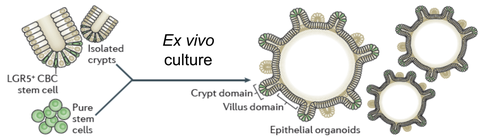
- What are the molecular mechanisms responding to CSC depletion?
- Are molecular features conserved between primary and metastatic tumors?

RECAPITULATING HUMAN CRC IN MOUSE

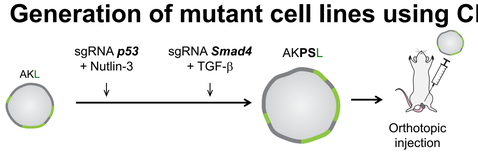
1. Model of intestinal tumorigenesis



2. Epithelial organoid culture



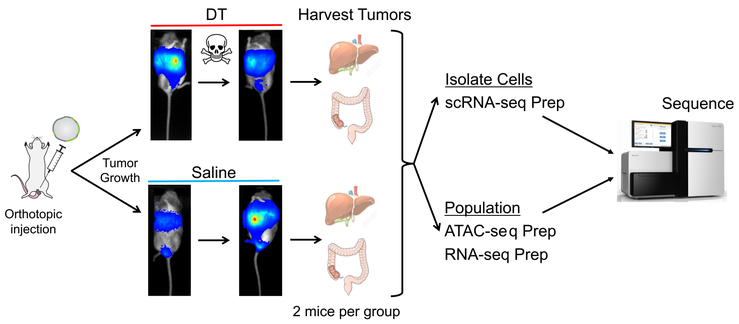
3. Generation of mutant cell lines using CRISPR/Cas9



- *Amenable for long term DT treatment*
- *Longitudinal tumor follow up*

DATASET GENERATION

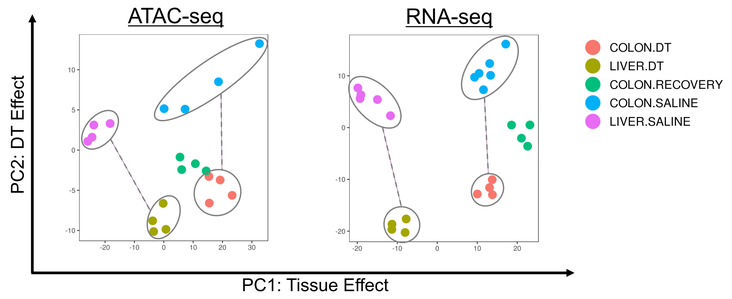
1. Utilizing a multi-omics approach to study CRC



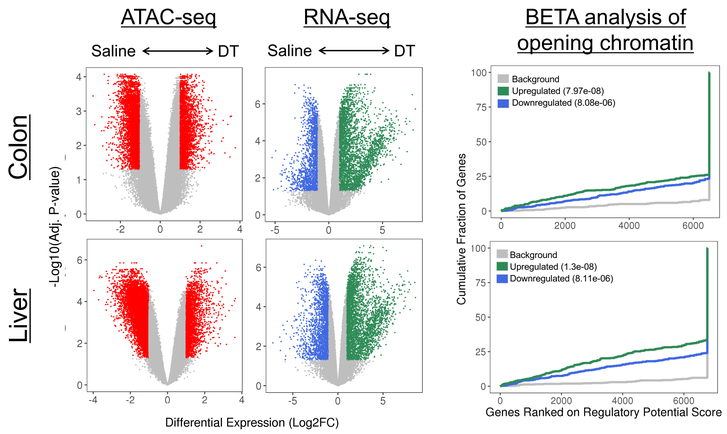
- To generate a rich representation of the landscape of metastatic CRC, we pair population-level transcriptional data (RNA-seq) with data that assays the chromatin landscape of the same tumors (ATAC-seq).
- Single cell RNA-seq will help tease out whether differences in the cellular composition of tumors at each site could explain the distinct tumor behavior.

RESULTS

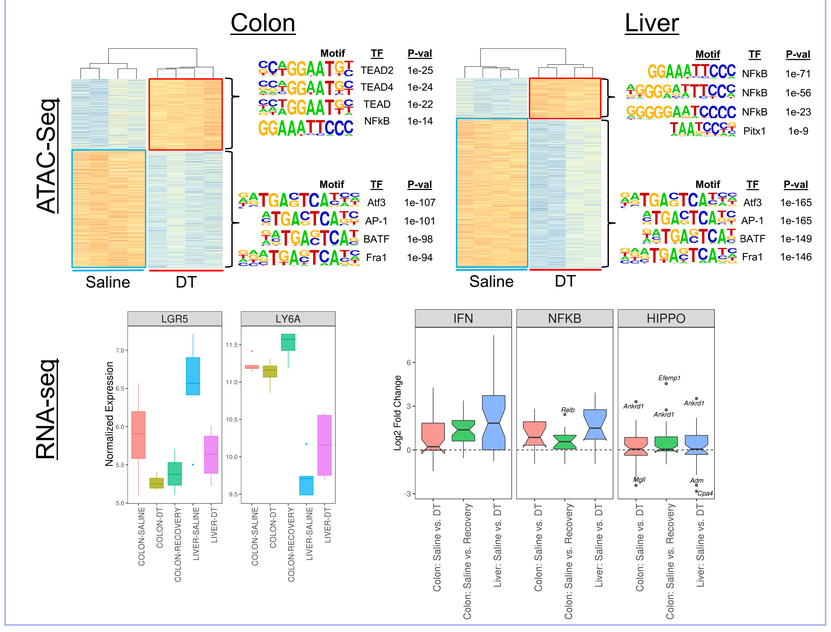
1. Strong changes in the transcriptional and chromatin landscapes are observed upon cancer stem cell depletion



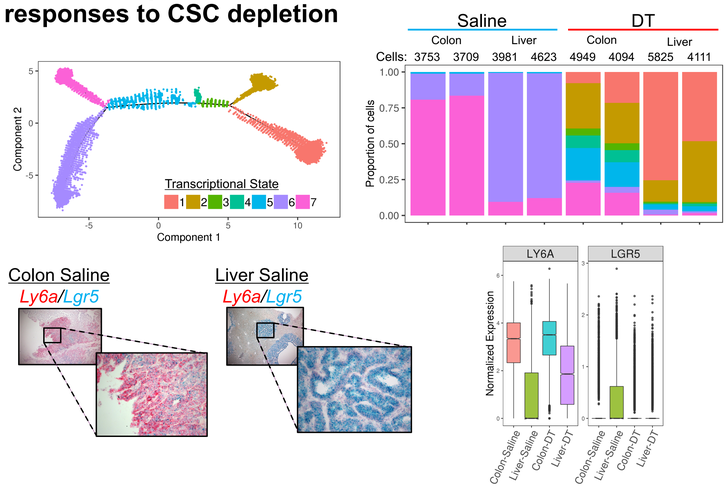
2. Changes of chromatin accessibility upon cancer stem cell depletion correlate with changes in gene expression



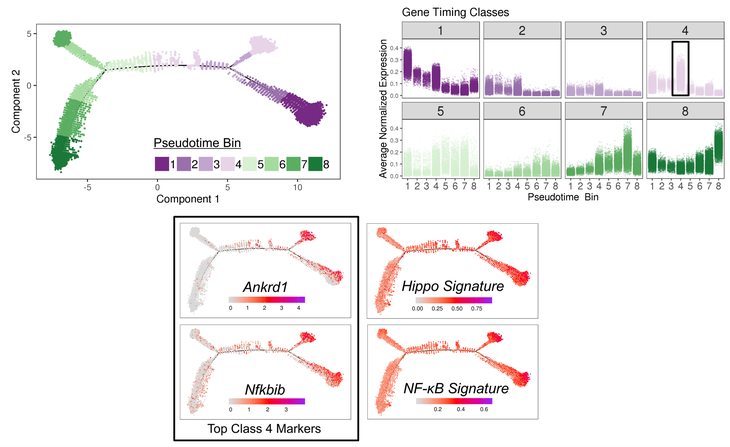
3. DT treatment induces NF-κB, Hippo and inflammatory response pathways



4. Colon tumors and liver metastases differ not only upon stem cell depletion but also at baseline and exhibit different responses to CSC depletion



5. Unbiased identification of gene timing classes suggests a role for Hippo and NF-κB pathways in CSC plasticity



Conclusions

- Our results suggest that Interferon response, NF-κB and Hippo signaling pathways are induced upon DT treatment
- We identify shifts in cell composition of tumors at the primary and metastatic sites
- Our work offers insights into the mechanisms underlying tumor cell plasticity which represent a challenge for cancer treatment and opportunity for drug discovery

Future Directions

- Better understand how primary tumors respond to stem cell depletion compared to the metastatic setting
- Address if the system returns to a steady state after DT treatment arrest

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