Anthony Gavalas Group – PhD Project 1

Adult pancreatic centroacinar cells as cells of origin of pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) represents over 90% of pancreatic cancer cases and it is among the most lethal forms of cancer. Kras mutations (Kras*) that result in permanent activation of the protein are the initiating event in more than 90% of PDAC cases and are required for tumor maintenance. The cells of origin of PDAC remain unknown and this hinders efforts to identify early molecular markers of the disease and understand the core molecular machinery of the transformed cells. Effective targeting of this machinery will help treat the disease and limit the possibility of relapse.

Strong candidate cells of origin would be adult progenitor cells that are mitotically active, and already express Kras. Previous work in our lab showed that Aldh1b1-expressing centroacinar cells (CACs) fulfill these criteria. Additionally, we have found that a functional Aldh1b1 is necessary in a PDAC mouse model for the development of the disease. To evaluate whether PDAC may originate from these cells and elucidate the implication of Aldh1b1 function, we have generated and validated several new mouse models. Ongoing work with these mouse models indicates that the targeted expression of Kras* in Aldh1b1^{+} CACs results in PDAC. Isolated and expanded in vitro Kras* / Aldh1b1 expressing CACs give rise to after orthotopic transplantation in immunocompromised mice.

The project will develop along three axes (a) conclude the experiments described above which establish that Aldh1b1 expressing CACs are cells of origin of PDAC (b) use both genetic and metabolic analyses of in vitro expanded CACs to identify the molecular mechanisms implicated in the Aldh1b1 mediated oncogenic transformation of CACs (c) analyze the early transcriptome and chromatin changes accompanying this process to identify the gene regulatory networks driving this process. The combination of these experiments will identify regulatory networks that would be potential targets for PDAC therapies.