Role of the class IA PI3K p110β subunit in pancreatic cancer

ARCUCCI S., THERVILLE N., BASSET C., VERTUT A., GUILLERMET-GUIBERT J.

(1) CRCT, Cancer Research Center of Toulouse, France

**Purpose:** PI 3-kinases are key signal transduction enzymes which are generally considered to be excellent new targets for therapeutic interference. PI3K signaling is altered (constitutively active) and correlated with a poor prognosis in pancreatic ductal adenocarcinoma (PDAC)\(^1\). Transdifferentiation of pancreatic acinar cells in duct-like cells is at the origin of pancreatic ductal cancer and there is strong evidence of the implication of PI3K signalling pathway in duct formation from exocrine acinar cells during the biological process called Acinar to Ductal Metaplasia (ADM). We have previously demonstrated that the isoform alpha of PI3K is necessary for the transformation of acinar cells by oncogenic Kras\(^2\).

Given that the function of p110β in pancreatic cancer cell is unknown, the aim of our project will be to study the role of p110β in the initiation and progression of this cancer.

**Experimental Design:** We analyzed the biological impact of pancreas-restricted genetic inactivation of p110β during pancreatic cancer initiation induced by oncogenic Kras with or without mutated p53. In particular, we searched the mechanisms of action of p110β in pancreatic cancerogenesis and in ADM formation.

**Results:** We found that genetic inactivation of the p110β isoform does not prevent in vivo the formation of ductal structure. However, mice harboring genetic inactivation of p110β in their pancreas are protected from mutated Kras and p53-induced lethality. Moreover, p110β inactivation in pancreatic epithelial cells is responsible for changing the immune cell recruitment and the stromal response to epithelial oncogenic Kras signal or to inflammation.

**Conclusion:** Our data suggest that p110β genetic inactivation in the pdx1-positive cell lineage (pancreatic lineage) plays an important negative role in murine pancreatic cancer initiation induced by genetic alterations commonly found in pancreatic cancer.

**References:**