Dual metabolic functions of group IV cytosolic phospholipase A2 alpha (cPLA2α) in pancreatic ductal adenocarcinoma

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Purpose: Pancreatic ductal adenocarcinoma (PDAC) is a fatal disease, the 5-year survival rate of patients after diagnosis is 8.2%. Its aggressiveness is in part due to its dense stroma, mainly composed of cancer associated fibroblasts (CAF) and macrophages, which limits oxygen and nutrient supplies to tumor cells. Despite these harsh conditions, tumor cells survive by modifying their metabolism to meet their energy and biomass needs. Hence, identifying the metabolic pathways crucial to PDAC remodeling remains an interesting strategy to find new treatments against PDAC.

Experimental Design: Pdx1-Cre; Ink4a/Arffl/fl, LSL-KrasG12D mice developing spontaneous PDAC were used to define metabolic signature by transcriptomic and lipidomic approaches and identify metabolic therapeutic targets as cPLA2α which is highly represented in PDAC, as well as their substrates, the arachidonic acid (AA) present in membrane phospholipids (PL).

Results: The AA, released from PL by cPLA2α, serves as precursor of the synthesis of prostaglandins (PG) and leukotrienes (LK), implicated in cancer cell survival and metastasis spreading. We showed that cPLA2α, in patient’s PDAC, is present at high rates both in tumor and stromal cells, while, in vitro, stromal cells showed higher cPLA2α levels than tumor cells. This led us to the hypothesis that stromal cells can provide cPLA2α to PDAC cells. We showed that cPLA2α is well present in extracellular vesicles (EV) produced by patient-derived CAF and/or macrophages and these cPLA2α-loaded EVs are rapidly taken up by human tumor cells. Now, it remains to determine the impact of this EV-dependent cPLA2α trafficking on proliferative and metastatic capacities of tumor cells. In addition to its implication in PG and LK synthesis, we suspected that cPLA2α, through its interaction with NADPH oxidase 2 (NOX2) identified by the superimposition of our microarray dataset to a murine interactome, may be also involved in NOX-driven superoxide production. We already validated cPLA2α-NOX2 interaction in PDAC cells, as well as in CAF and macrophages, and showed that co-expression of their respective transcripts is correlated to poor patient outcome.

Conclusion: Taken together, our results suggest that disrupting the metabolic dialog, involving cPLA2α and/or its interaction with NOX2, between stromal and tumor cells could be potential therapeutic strategies to fight PDAC and improve patient survival rates.