Aggressive PDAC with high levels of circulating DNA requires PI3K isoform alpha to accelerate metastatic disease.


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**Purpose:** Pancreatic adenocarcinoma (PDAC) is characterized by a late detection and the lack of efficient treatment leading to a poor prognosis. Circulating cell-free DNA (cfDNA) has been associated with poor prognosis in PDAC (1). PI3Kα is one of the 4 class I PI3K isoforms and is crucial for PDAC development (2). In this study, we deciphered the role of PI3Kα in PDAC progression and the potential of its pharmacological inhibition to reduce metastatic burden.

**Experimental Design:** We used a preclinical model of double transgenic mice (KPC) harboring Kras and p53 mutations under the expression of Pdx1, a pancreas-specific promoter, which spontaneously develop metastatic PDAC. PI3Kα targeting was realized with BYL719 treatment after the detection of a mass. A panel of inhibitors was used including global, α-specific, β-specific, γ-specific and β/δ-specific inhibitors on a panel of murine, human cell lines and patient primary cultures.

**Results:** KPC mice with high level of cfDNA were found as more aggressive, with higher number of metastasis sites and decreased survival. Interestingly, primary tumors from pancreatic cancer metastatic patients compared to localized tumors presented a molecular signature linked with PI3Kα activation. This signature was searched in patient-derived ascites primary cultures from PDAC and preclinical models. A non-linear correlation was found between the IC50 of PI3K inhibitors for the α isoform and their capacity to inhibit cell motility and migration, to induce cytotoxic effects and to inhibit Akt phosphorylation on Ser473. Similar results were obtained with siRNA and in PIK3CA oncogenic cell lines suggesting that PI3Kα controls pancreatic tumor cell line motility and migration, regardless the driving oncogenic mutation. Finally, treatment of KPC mice with BYL719, a PIK3α specific inhibitor, inhibited tumor growth, metastasis and the development of ascites, while decreasing the amount of cfDNA.

**Conclusion:** PI3Kα drives PDAC progression and leads to aggressive disease. The pharmacological inhibition of this isoform prevents metastasis in KPC mice and thus constitutes a promising therapeutic strategy to improve PDAC management.

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**References:**


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